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PROCEEDINGS

of

Teachers Seminar On Pharmacology

And Related Subjects

VOLUME II

Held Under The Auspices

of

The American Association of Colleges

of

Pharmacy

at

Purdue University School of Pharmacy

July 9-14 inclusive, 1951

Edited By

Glenn L. Jenkins

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By The Support Of

THE AMERICAN FOUNDATION FOR PHARMACEUTICAL EDUCATION

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FINANCIAL SUPPORT FOR INSTRUCTION AND RESEARCH

W. Paul Briggs
Executive Director, American Foundation for Pharmaceutical Education
1450 Broadway, New York 18, N. Y.

Last week, on July 4th, we celebrated the one hundred and seventy-fifth year of our independence as a nation. We gained our national independence after a violent struggle and we have preserved it over the years by the righteousness of our cause and our willingness to fight, if necessary, to retain it. Even the currently popular "one world" ideology probably will not disturb the security of our independence at the national level.

While the independence of the nation was being strengthened the independence of the individual and the independence of scholars has been threatened. Your freedom in the classroom and in the research laboratory is not as secure as our collective freedom as a nation. Obvious economic forces and subtle pressures from various sources could place your teaching and your studies under intolerable restrictions. Much of America's greatness is due to free education and freedom in education. Our technological, medical and industrial achievements could not have been attained under a system of regimented research. Education cannot be accomplished by adherance to discredited dogmas and rigid rules.

The American Foundation for Pharmaceutical Education is dedicated to "the upholding, improving, broadening and promoting of pharmaceutical education; and to aiding in the creation of sources of unbiased and authoritative investigation and experimentation on pharmaceutical problems." The Foundation undertakes to carry out these and other objectives, in part, to insure your continued freedom as scholars and teachers. The future of pharmacy and pharmaceutical education, indeed the future of America, rests, in substantial degree, upon the independence of our educational systems. And the future of the Foundation rests upon the degree of financial support which an enlightened and generous industry can provide.

Benjamin Rush warned that "to be long-lived, republics must invest in education." America has long placed its faith in education and annually invests five billion dollars for this purpose. Individuals and the federal, local and state governments do not make this investment on faith alone but, in large measure, because of the convincing evidence that education is a sound and profitable investment. The drug industry should not be asked to support pharmaceutical education on faith alone. Happily this is not necessary. There is abundant tangible evidence to prove that funds well invested in pharmaceutical education produce profits to donors. Many of you have directly or indirectly provided some of this evidence through your own research, through well-trained graduate students and better-trained practicing pharmacists.

In my view, the Foundation is so vital to all phases of pharmacy that it will flourish, and in turn it will insure continued improvement, expansion and independence to instruction and research in pharmacy. Certainly this is our goal and I confidently believe it will be achieved. Largely through the devoted work of the late Dr. E. L. Newcomb, with the

financial support of the drug industry, the Foundation has already done much to advance pharmacy.

While educational values cannot be measured in dollars, I think you will be interested to know that the Foundation has already contributed well over a million dollars to the cause of pharmaceutical education. The Foundation carried the entire cost of the Pharmaceutical Survey, amounting to nearly $200,000. This study was requested by the A.A.C.P. and its influence for good is already apparent. Much of the work of the Survey was concerned with educational matters and we hope that, as teachers and administrators, you will make maximum use of the Survey findings. The Foundation, through the Survey, financed the extensive study of the pharmaceutical curriculum by Dr. Lloyd E. Blauch, Assistant Director in charge of Curriculum Studies and the A.A.C.P. Committee on Curriculum headed by Dr. George L. Webster. This report, which will be available in the near future, should exert a profound influence on the future pattern of pharmaceutical education.

The Council on Pharmaceutical Education is one of the most critically important instruments for the advancement of pharmaceutical education. In recognition of the essentiality of its work, the Foundation has provided the necessary financial support to expand the constructive activities of the Council. The Council on Pharmaceutical Education was established in 1932 while the Council on Medical Education was created 28 years earlier in 1904.

The Carnegie Foundation for the Advancement of Teaching published its report on medical education, the Flexner Report, in 1910. The Report of the Pharmaceutical Survey was published in 1949. When the Flexner Report was published the number of medical schools had dropped from 446 to 162 and these were said to range in quality from good to disgraceful. Today there are 72 accredited medical schools and almost an identical number of accredited pharmacy schools. From this it will be seen that constructive actions to improve pharmacy education have followed similar actions in medicine by from 28 to 39 years.

The impact of the Pharmaceutical Survey and the new accreditation standard of the Council on Pharmaceutical Education will further strengthen pharmacy education just as the Flexner Report literally redeemed medical education. Whether we can, should or will continue 70 colleges of pharmacy cannot yet be determined. But it is already apparent that, in faculty, physical facilities, curriculum, libraries, student selection, graduate training, indeed in every aspect, pharmacy education today is vastly and encouragingly superior to that of even five years ago.

One may rightly expect the next five years to produce major advances, as the programs of the Foundation-supported Council and the curriculum study are accomplished. Application of the new and higher accreditation standards and establishment of a more effective training program may result in a redemption of pharmacy education parallel to that which was achieved for medicine by the Flexner Report.

Dean Jenkins, in announcing this seminar, wisely embraced the opportunity to inform drug industry leaders about the project. He established the place of the Foundation as sponsor and invited attendance and partici-

pation from pharmacologists in industry and government. I hold some reservations on the possibilities of a utopian world fellowship alliance but none about the dynamic effectiveness of an all-inclusive drug industry alliance. Dean Jenkins made a real contribution in this direction and advanced the cause and the security of the American Foundation for Pharmaceutical Education.

This is a splendid example of the kind of team play so necessary to keep funds flowing into the Foundation, which in turn, are used to strengthen your academic programs. Heavy demands for support from worthy agencies are almost daily directed to the drug industry. The American Foundation for Pharmaceutical Education needs your help to keep its needs before current and potential patrons. But far more convincing to business men is evidence of benefits and accomplishments of the Foundation.

Each of you can contribute to the success of the Foundation, your institutions and your own academic freedom by embracing every proper opportunity to focus public and industry attention on the productiveness of the Foundation's programs. For example, it would be mutually helpful to widely distribute to industry abstracts or full reprints of worthwhile research done by Foundation Fellows; to identify in your press releases as former Foundation Scholars or Fellows your graduates who may be elected or appointed to state association or other offices and positions; to tell your friends in industry of the value of Foundation support to activities in which you have a special interest such as the Journal of Pharmaceutical Education, the Pharmaceutical Survey, and this seminar.

I am not asking you to do my job, which in large measure is concerned with maintaining the interest and support of industry. The Foundation will do this as effectively as possible but with scores of "causes" fighting for industry's support we need the united strength of the "Minute Men" of pharmaceutical education. You need not fire a shot that will be heard 'round the world and turn the "Red Coats" back, but you can carry the banner of the Foundation and thus help keep the red ink out of our books. Actually, you and your academic colleagues are the field sales force of the Foundation. The colleges of pharmacy are the manufacturing plants of the Foundation. You produce the end products of the Foundation -- better pharmacists, better teachers and better laboratory workers. To keep our "educational industry" moving forward we need the benefit of your sales promotion effort.

After three hectic months I am more than ever convinced that the American Foundation for Pharmaceutical Education will become increasingly important to all pharmacy. I am optimistically confident that it will attain a financial strength to enable it to protect the independence of instruction and research in pharmacy in the uncertain years ahead. The Foundation is maintaining every program it has started, and is doing so at the same or at a higher level than in the past. But there is yet much to be done to carry pharmaceutical education and research to its proper position. On behalf of the Board I can assure you that the Foundation is solidly behind every justifiable, worthwhile movement to strengthen and advance pharmacy in general, and pharmaceutical education in particular.

The Board of Directors on May 17, 1951 approved a budget for the coming year of nearly a quarter of a million dollars. This will provide

undergraduate scholarships in every accredited college of pharmacy; sustain approximately 100 graduate Fellows in 21 colleges; contribute substantial support to the American Council on Pharmaceutical Education; underwrite the operating deficit of the American Journal of Pharmaceutical Education; allow for continuance of the summer teachers seminars and the other activities of the Foundation.

Even in these days of astronomical budgets a quarter of a million dollars is a sizeable sum. But it is by no means too much, or even enough, to carry out the objectives of the Foundation, or indeed to meet the minimum needs for professional education in pharmacy. We hope to materially increase our annual income from contributions and to then increase in scope and in quantity the Foundation's support to education.

Having been a college of pharmacy Dean I am painfully aware of the hazard of asking teachers if they need money to carry out new plans. Your very presence at this seminar proves your alertness and I am sure each of you have valuable ideas for improving your teaching and research. I know that few, if any, such plans can be carried out without money. Since a part of my job is the raising of money, I am cautious about inviting new suggestions for spending. However, the Foundation wants to do everything in its power to strengthen your work and you are the ones who know what should be done.

Without the slightest suggestion of a commitment, I invite you to tell us how the Foundation can better attain its objectives in the future. We will welcome your suggestions and we will be especially pleased to have detailed plans through which the Foundation can participate in really significant improvements in pharmaceutical education. To paraphrase Benjamin Rush, "To achieve its rightful place and be long-lived, pharmacy must invest in education". The American Foundation for Pharmaceutical Education was created by the National Drug Trade Conference representing every segment of the drug industry. I am sure that the entire industry subscribes to the doctrine that the future position of pharmacy will be determined by the strength of its educational system. I am equally sure that the industry will support, to the full extent of its capacity, worthwhile movements to maintain pharmacy's rightful place and long life.

I am glad of the opportunity to be with you on this occasion. Your program gives every evidence that your sessions will be productive. Pharmacy can well be proud of your past accomplishments and can look forward with confidence to even greater achievements in the years ahead. And the American Foundation for Pharmaceutical Education will be working with you to attain our common objective of a preeminent position for pharmaceutical education.

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QUALIFICATIONS OF THE INSTRUCTOR OF PHARMACOLOGY

Harald G. O. Holck
University of Nebraska, College of Pharmacy

Introduction

The importance of the influence of the teacher upon the student was emphasized by the zoologist, David Starr Jordon, when he said: "Have your university in sheds, have it in tents, but have the masters there." (1) It thus seems of the greatest importance to secure the best teachers available for the teaching of pharmacology. However, it must also be emphasized that no one can continue as a 'master' unless interested in retaining this status and unless given reasonably good facilities by which he can constantly continue his development.

Inasmuch as time will allow discussion of only selected phases of the subject, we have presented in an appendix three lists of qualifications of a good teacher: one presented by Professor M. O. Pella last year at Atlantic City (2); one by Dr. D. A. Worcester, Professor of Educational Psychology and Measurements; and one by Dr. E. Roger Washburn, Professor of Chemistry. The latter two lists were recently discussed at a symposium sponsored by the University of Nebraska chapter of the American Association of University Professors.

Training and Experience of the Instructor

All lists of qualifications of a good instructor agree that he must know his field of teaching. To meet this qualification it seems essential that he must hold a doctor of philosophy degree based on work in pharmacology and related sciences. To keep abreast of what is going on in pharmacology is in itself a Herculean task. The fast and furious pace in this field is shown by the fact that the second edition of a well known textbook, which first appeared just two years ago, is 123 pages larger than the first edition, an increase of nearly thirteen per cent. Not only must the instructor in our subject attempt to keep up with pharmacological progress, but he must also try to keep well informed in associated sciences, notably in physiology. In view of this, it was most astounding to note that, according to the report of Dille in 1938 (3), in 17 out of 25 schools of pharmacy in which pharmacology was being offered at that time, the instructor was asked to teach from two to five additional subjects, and in four cases even more. Although this situation has improved considerably since then, the Utopia of a full-time pharmacologist in every college of pharmacy has not yet been attained. However, the progress made in this direction and the plans for the next few years indicate that deans and directors have become more and more aware of the need for protecting the instructor's time so that he may do more productive work; this is all the more important if he also is responsible for graduate teaching.

Importance of History in Pharmacology. The general means by which the instructor may keep up with recent advances by reading of texts, reviews, journals, etc., were in a large part presented yesterday in our discussion of the didactic work in pharmacology and need not be repeated here. However, we wish to dwell a little more upon the importance of the instructor's having knowledge of the historical development of pharmacology, as yet a young science, as a requisite part of his being well

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versed in this field. As more discoveries are made, an increasing amount of time will be required for acquiring this historical background. This is especially true because the real scholar must transport himself back into the era of development preceding the establishment of specific chairs in pharmacology and must view his field in relation to the state of development of science and culture of that period.

To stress the importance of the historical development of pharmacology upon the prospective teacher, we included in our seminars in pharmacology for graduate students this year the presentation of the contributions of Andreas Vesalius, Claude Bernard, Rudolf Magnus and John Jacob Abel. Outlines of each of these presentations are available here in case anyone wishes to examine them. In these seminars many features of the lives of these men as teachers were brought out, first of all in relation to how they modified the trends of teaching in their day. Thus, Vesalius started a veritable revolution in teaching by personally taking over the demonstrations in anatomy, previously conducted by barbers who were often inept, and by urging the student to make observations for himself, rather than accepting the dicta of the old authorities, especially those of the famous Galen. Bernard, the prince among the French physiologists, helped establish physiology as an independent science, while simultaneously initiating early beginnings in pharmacology in his classical work upon curare and carbon monoxide poisonings. Magnus was the great luminary in creating student enthusiasm in pharmacology. At Lincoln, the students turn out en masse to welcome the returning Cornhuskers after a football victory; when Magnus returned to Utrecht after the first World War, he was given a similar rousing student welcome and escorted from the railroad station to the pharmacological institute. Unless he were in a casket, and some students may wish he were, would a group of students in our day even assemble at the station to mark a professor's return from a leave of absence? In the fourth seminar emphasis was placed on the major contribution of Abel, who, from meager beginnings, succeeded in establishing experimental pharmacology upon a firm basis as a teaching tool.

In our course in pharmacology we attempt to imbue the prospective teacher, even as an undergraduate student, with interest in and love for a broader and deeper knowledge of his subject. The story of how Banting and his associates succeeded in preparing insulin because of Banting's contempt for the negative results of the past lends itself well to that purpose. The value of this presentation is endorsed by the inclusion of the major part of Banting's own description of his discovery in a recent textbook.

Importance and Advantages of Attending Conventions. The successful instructor naturally wishes to attend and participate in the teachers' conferences of the American Association of Colleges of Pharmacy. He should not only be urged to do so, but should be granted financial aid for this purpose so that he may become acquainted first hand with trends in teaching methods as well as with his teaching confreres. Of course, the same thing holds true for a seminar of the type now in progress here.

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tunities offered to visit the pharmacological laboratories of the schools in the convention city, listens to descriptions and discussions of new discoveries by the men who made them, and, of special importance to teachers in pharmacy colleges, learns directly about what is going on in related fields of scientific endeavor. Assuming that he already holds a Doctor of Philosophy degree in pharmacology, it is hoped that he is of the type that not merely "chirps, but also scratches," so that he will present results of his own research at such conventions.

Inasmuch as research of the highest caliber is carried out by most of our pharmaceutical manufacturing houses today under the leadership of gifted directors, the teacher often accepts invitations to visit nearby commercial research laboratories. Techniques not available in many colleges of pharmacy and experiments in progress may be studied. The directors of these laboratories not only supply expert guidance, but give advice based upon their experience to make such visits even more worthwhile.

Ability to Select Material Most Useful to his Students

Let us assume that the good teacher constantly strives to broaden his knowledge of pharmacology by reading, research and attendance at conventions. He then must exercise his critical ability to sift from all of this knowledge the material to be presented to his students, most of whom will enter retail pharmacy rather than careers in teaching or research. Once he has completed the arduous task of preparing a well-rounded course, it would seem unnecessary to make up a new set of lectures every year. However, the teacher must constantly revise his material, not only to incorporate the important new drugs and delete those becoming obsolete, but to make adjustments for the results of his previous teaching as shown by examination results. He should not only be self-critical, but should welcome the criticisms of others. It is impossible for him to rectify all the deficiencies in the previous training of each and every student. However, he is favored by the fact that students not well suited to the pharmaceutical field have not been allowed to continue in school, hence, will not be enrolled in the course in pharmacology. Nor will the instructor be able to overcome all the handicaps entailed in the great variation in the number of hours devoted to outside work by his students; these difficulties have been increased by early marriages. When a student has to work every night to support a family and has been kept awake by a teething baby he is apt to fall asleep during the early morning lectures. In view of these added difficulties, it becomes all the more important that the teacher in revisions of his lectures constantly attempt to find means of making them clearer, more interesting and more inspiring, and of such a nature that they will induce the student to think for himself--the ultimate goal of education.

Ability to Arouse and Maintain Student Interest

The instructor must at all times guard against permitting his lectures to degenerate into a purely mechanical process by which the material in his notes is transferred to the notebook of the student without passing through the minds of either.

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Proper Use of Texts and Library Facilities. To prevent his students from becoming automatons that merely regurgitate the lecture material in response to examination questions, the teacher must in his lectures stimulate interest in using the assigned textbooks. This is of paramount importance to students who learn rather slowly, or have difficulty in recording adequate lecture notes. By announcing in advance the topics to be covered, the instructor enables the students to read the appropriate material in the text and thus to come to class much better prepared to understand the lectures. This applies even more to students coming from foreign countries, because they may have difficulty in following a lecture in an alien tongue. This difficulty is increased if the teacher also hails from a foreign land. Distribution of a condensed version of the first lecture serves partially to guide the student in learning how to concentrate the lecture material in outline form in his notebook for future use and partly to allow him to become acquainted with the voice, method of presentation, and personality of the instructor. The good teacher must also insist that the student actually read the references given to him as sources of information needed in answering questions asked in the laboratory manual. This is very difficult to accomplish, especially since it is so much easier to copy such answers from notebooks of former students! Although the student may not, after graduation, have frequent need to visit a scientific library, it is of great value to him to learn how to find specific information under the guidance of expert and willing librarians. This experience may be of considerable use in his professional life.

Development of a Sense of Civic Responsibility

The instructor must keep in mind that his students, upon graduation, will enter their professional careers, not only possessing considerable knowledge of pharmacology and other professional subjects, but as educated men and women. As such they must, as members of society, develop a strong sense of civic responsibility and take an active interest in many problems involving the welfare and progress of the community in which they live. From his own knowledge and observations, it is entirely possible that the professor may have acquired certain strong convictions concerning many sociological problems, such as that of alcoholism. However, he should remember that fanaticism will not solve such a problem. He must, rather, place before his students all of the scientific facts and sociological implications of the problem and then encourage them to determine for themselves, on the basis of this information, the best way to assist their fellow members of society in coping with this great problem. The knowledge and critical attitude which they have acquired in their study of pharmacology should be extremely helpful in this connection.

understands new terms, but learns to spell them correctly and knows their derivations. Attention of and interest on the part of the student are not in themselves enough. Recall and recognition of terms and principles are equally important. Knowing the etiology of the new terms helps in this. The teacher must also make certain that the student sees the proper relation to physiological principles and to the disease for which the medicament is advocated. However, some degree of caution should be observed in reviewing material from physiology, pharmacy, or other fields to avoid devoting an undue proportion of the time allocated to the course in pharmacology. Undue duplication of material given in preceding courses is to be avoided, lest the repetitions become boring to the student.

Proper Use of Texts and Library Facilities. To prevent his students from becoming automatons that merely regurgitate the lecture material in response to examination questions, the teacher must in his lectures stimulate interest in using the assigned textbooks. This is of paramount importance to students who learn rather slowly, or have difficulty in recording adequate lecture notes. By announcing in advance the topics to be covered, the instructor enables the students to read the appropriate material in the text and thus to come to class much better prepared to understand the lectures. This applies even more to students coming from foreign countries, because they may have difficulty in following a lecture in an alien tongue. This difficulty is increased if the teacher also hails from a foreign land. Distribution of a condensed version of the first lecture serves partially to guide the student in learning how to concentrate the lecture material in outline form in his notebook for future use and partly to allow him to become acquainted with the voice, method of presentation, and personality of the instructor. The good teacher must also insist that the student actually read the references given to him as sources of information needed in answering questions asked in the laboratory manual. This is very difficult to accomplish, especially since it is so much easier to copy such answers from notebooks of former students! Although the student may not, after graduation, have frequent need to visit a scientific library, it is of great value to him to learn how to find specific information under the guidance of expert and willing librarians. This experience may be of considerable use in his professional life.

Development of a Sense of Civic Responsibility

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Stimulation of Continued Interest in Pharmacology

The good instructor who has chosen pharmacology presumably because of his interest in and enthusiasm for this field, should, if he is a successful teacher, be able to impart some of his fervor to his students. The extent to which he succeeds in this depends largely upon the attitude which the instructor takes toward his work. He must not only be inwardly enthusiastic, but he must reflect it at all times, for enthusiasm is contagious. Should he, at any time, approach his tasks with an attitude of complacency or boredom, this attitude will very quickly be transmitted to his students. It is only by example that he can instill in them a strong desire to continue to study critically progress in this field after graduation. This means more than reading material supplied by manufacturers and their sales representatives, excellent as such presentations usually are. It is always a pleasure, and a measure of the success of the instructor, to have former students return to him for counsel, showing that they have retained their interest in pharmacology.

Opportunities occur for the teacher of pharmacology to present discussions of recent advances at state or local pharmaceutical meetings. In some localities interest on the part of former students, in keeping abreast with the march of pharmacological science, has led to organized contact with the instructor in the form of brief refresher courses.

Guidance of Student Learning

The good teacher recognizes a major responsibility in dealing with questions raised by his students, and especially those stimulated by their failure to answer satisfactorily specific examination questions. It is, of course, very simple to supply the student with the correct answer. But it is much more helpful if the teacher attempts to direct the student's thinking so that he may have a full understanding of the principle involved and be able to apply it to similar problems. With large classes, time may not be available to do this with every student. It was for this reason that we proposed in our discussion yesterday that the instructor spend a part of a lecture period after each examination explaining to the class the objectives of the questions requiring thought, rather than rote memory or recall. Inasmuch as inadequate answers do not necessarily imply that the student is deficient in reasoning power, but may suggest that the subject matter was improperly presented in the first place, or that the statement of the question lacked clarity, the wise instructor is careful not to single out any student by name because of incomplete, poor, or even unusual answers. Nor should he read answers by the best students, mentioning their names and expressing praise for their efforts. Such criticism or commendation should be reserved for private conferences, and even under these conditions, either should be used in moderation. If, in an extreme case, the instructor elects to read an unsatisfactory answer in class without identifying the student, he must carefully guard against adopting a satirical attitude. Even though the student is not identified in class, he will, nevertheless, recognize the answer as his and is likely to resent the criticism as applying to him personally. As a general policy, the considerate instructor should avoid verbatim readings of answers in class, regardless of whether they are right or wrong.

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would understand what he said, another third would get a 'muddled' idea of what he was trying to explain, and the last third would gain just the opposite understanding. Although this may be an exaggeration, the good instructor realizes only too well, with human nature what it is, that he must condone a student for trying to supply an answer to a question, although he has failed completely to grasp the principle involved, and, as a consequence, his answer bears no relation whatsoever to the question. Such answers indicate that the student wishes to show the teacher that he knew some part of the assignment, although not the one covered by the question. Of course, the good teacher must attempt to curb this tendency to dodge issues, even applying penalties by making subtractions for such answers, if necessary. Even under these conditions, he will continue to encounter difficulty in preventing students from guessing in the absence of specific knowledge or proper reasoning power. This is, after all, just another confirmation of the truth of the adage that 'a drowning man will grasp at a straw.'

Sympathetic Attitude Toward Students

The good teacher must have a great deal of sympathy for and understanding of the student and his problems. This applies not only to the immediate problems connected with his scholastic difficulties, but to problems in a number of other areas. Usually, the professor is not in position, nor is it his function, to render direct financial aid, although this is sometimes done in emergencies which may arise. In any case, the professor does everything possible to assist worthy students in obtaining scholarships, grants, or loans which may be available. He shows a sympathetic attitude toward the student in case of illness or other misfortunes; he helps him study the material missed because of the resulting absences from class; he shows him how best to prepare for examinations, realizing that with a number of classes scheduled in regular sequence, the student is unable to follow the excellent pedagogical principle of reviewing the lecture within the hour immediately following and again the same evening. The instructor tries to adjust his schedule for examinations, whenever possible, to avoid the possibility of his students having several major examinations on the same day. He should announce well in advance the date of each examination and outline clearly to the class the scope of the questions to be expected. He may find it useful to set aside a short period to allow students to ask questions concerning the general nature of the tests before they are given.

However, to insure that the student approaches the laboratory sessions with a reasonably clear understanding of what is expected of him, the instructor should at times give unannounced brief written laboratory quizzes, and the students should be informed at the beginning of the course that such tests may be expected at the beginning of any laboratory period.

Insistence of Proper Deportment

Regardless of how sympathetic the good teacher may be concerning all legitimate individual problems of his students, he must also recognize the fact that he has a responsibility to discharge in training his students, both by precept and example, in punctuality, courtesy, and gentlemanly behavior. Unless valid excuses are furnished, assigned tasks must be completed on time. The matter of decorum involves the student's

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behavior both in and out of class. Upon graduation, the student is expected to be not only a technically educated person, but one of culture, as well.

If, in the classroom and laboratory the reins are held too loosely, undesirable frivolity is quite likely to make its appearance. When once we saw a student place a dead rat in the pocket of a classmate, proper steps were taken to prevent the recurrence of similar juvenile impulses. On another occasion, while we were laboring to get a demonstration to proceed properly, we noticed one of the better students dropping paper wads down the neck of a less gifted student who was making a sincere effort to gain an understanding of the experiment. A friendly talk with the offender, after letting him wait overnight in anticipation of a 'Hell and Maria' session, convinced him that we would appreciate his cooperation in preserving a dignified atmosphere in the laboratory. Fortunately, most students are capable of sizing up their teacher quite accurately and seem to know intuitively that certain patterns of behavior will offend him, and govern themselves accordingly.

The Limitations of the Teacher

One of the rather serious problems facing the prospective teacher preparing himself for a career in pharmacology is whether or not he wishes to specialize in a particular area of the subject. If his decision is for specialization, he should recognize the fact that this probably cannot be done without sacrificing to some extent the attainment of a well rounded view of the field as a whole. Toxicology, bioassay, and endocrinology (the latter often considered as a branch of physiology), all constitute important divisions of the general field of pharmacology. Any one of these divisions, if the instructor elects to specialize in it, would require the major portion of his time in acquiring complete mastery of the subject. Thus, the proper understanding of bioassay has demanded an enormous increase in the use of statistical methods, both in planning the assays and analyzing the results. Ultimately, the teacher in pharmacology may be forced to depend upon consultants in statistics if he is to find time enough to keep up with progress in pharmacology in general.

Most teachers of pharmacology who have been in this field for some years have had no opportunity to take formal courses in educational techniques and procedures. Perhaps it would be worthwhile for a young man intending to enter this field of teaching to consider the possibility and potential value of courses in teaching methods, educational psychology, and allied subjects before initiating or completing his technical training in his chosen field. Every teacher naturally recalls those of his own teachers who most impressed him and appropriates their methods and techniques for use in his own presentations. As time passes, he learns new methods through his own experience, and strives to improve his teaching by reading about teaching methods, by consultation with experts in the field, and by attending regularly conferences of teachers in the pharmaceutical field.

The Teacher As An Example

During discussions concerning the proper handling of certain problems involving student conduct at the American University of Beirut, Lebanon, the importance of the influence of the teacher's example upon

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Conclusion

In this discussion, intended primarily for the graduate student planning to enter a teaching career in pharmacology, we have first emphasized the importance of proper preliminary and continued study in the field, including that of its history, and of active participation in conventions. We have next taken up the matters of selection of material for class use, of ability to arouse and maintain student interest, even beyond the school years, of teaching the student to use library facilities, and of guiding his learning. We have also stressed the matters of developing his sense of civic responsibility, of possessing a sympathetic attitude toward students with insistence on proper deportment, and of considering the limitations of the teacher, as well as of the teacher as an example. The material has been supplemented with an appendix containing three lists of qualifications of a good teacher.

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1. Payne, F. and Spieth, E. W., An Open Letter to College Teachers, p. 181, The Principia Press, Inc., 1935.

2. Pella, M. O., American Journal of Pharmaceutical Education, 14, 426, 1950.

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APPENDIX A

BY H. O. HOLCK

THREE LISTS OF QUALIFICATIONS OF A GOOD TEACHER

The Good Teacher

Dr. Milton O. Pella
Professor, Department of Education
University of Wisconsin

1. The good teacher is a lady or gentleman possessing integrity of character and who is sincerely interested in helping others.
2. The good teacher is a scholar specifically and generally.
3. The good teacher possesses a balanced appreciation of his contribution to his department and the relationship of his department to other departments and to the total instructional plan.
4. The good teacher has a basic understanding of the psychology of learning and of educational principles.
5. The good teacher uses his knowledge of the psychology of learning and of educational principles in dealing with problems of learning.
6. The good teacher carefully selects, organizes and presents content in a clear logically organized manner.
7. The good teacher adjusts the presentation of material to the student's level of ability. He knows his students.
8. The good teacher stimulates intellectual curiosity in students.
9. The good teacher understands the several different methods of instruction.
10. The good teacher knows how and when to use each method of instruction.
11. The good teacher knows how and when to use tools of instruction.
12. The good teacher understands the function of tests as well as their limitations.
13. The good teacher knows how to construct a good test.
14. The good teacher is able to work with his colleagues in realizing the attainment of a common goal.
15. The good teacher is a research worker in the field of good teaching.
16. The good teacher is interested in progress.

What Makes A Good College Teacher

Dr. D. A. Worcester
Professor of Educational Psychology and Measurements
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Suggestions from recent graduates:

1. Must know his subject.
2. Must know something else.
3. Must like to teach

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4. Must know how to teach. (Not all use same method, but there must be some method).
5. Must know something about his students.
6. Must like students.
7. Should be still learning himself. (Not living merely in terms of his own profession and his own graduate research).
8. Must be open-minded. (Willing to listen to questions and willing to listen to opposing views. Willing to acknowledge errors).
9. Must remember students are learning and inevitably make some errors.
10. Must be interested in teaching students--not flunking them.
11. Should make clear, at an early date, the objectives of the course.
12. Should stick to these objectives.
13. Should not be far over the students' heads.
14. Should have a sense of humor, but this does not mean necessarily to tell a lot of jokes. Not take himself too seriously.
15. Should be accessible to students, in time and attitude.
16. Should let students know where they stand. (No mark below 4 and then fail).
17. Exams should be fair.
18. Exams should be in terms of the objectives of the course.
19. Should himself work.

WHAT MAKES A GOOD COLLEGE TEACHER

Dr. E. Roger Washburn
Professor of Chemistry
University of Nebraska

1. The teacher must desire to teach and be willing to work to satisfy his desire.
2. The students must desire to learn and be willing to work. The teacher should sustain and promote this desire and provide the opportunity for work.
3. The teacher must have a good knowledge of his subject; he should know much more about it than he can expect to teach.
4. Effort should be made to find out what the majority of the students in the class know about the subject so that too much time will not be devoted to review and so that the teacher will not start out too far ahead of his class.
5. Each course should be carefully planned, and the objectives should be definitely and clearly stated.
6. Each class meeting should be carefully planned, and in it some progress should be made toward the objectives of the course.
7. Assignments to the text or to reference material should be made; these should be definite, at least as to subject matter, if not as to pages or chapters.
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13. Examinations should not be limited to the objective type (multiple choice, true or false, fill in the blank, etc.) but should contain some questions requiring thoughtful discussion or logical development. The answers to such questions should be read by the teacher.
14. Research.
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THE ELEMENTS OF GOOD TEACHING

Paul Alexander
Professor, Department of Education, Purdue University
West Lafayette, Indiana

There is no one pattern of good teaching. Good teachers differ among themselves in personal characteristics and in their techniques and methods of instruction. Teaching is primarily a problem-solving situation. It includes competence in the determination of objectives, both ultimate and specific; an analysis of these objectives into a type or types of learning; and finally, the provision for learning activities by which the students attain these desired educational goals. The methods of a particular teacher, therefore, must be appropriate to his students, his subject matter, and himself. In all teaching situations, however, there are common elements of good teaching. These elements can be identified and, if recognized and understood, should contribute to a more effective solution of teaching problems.

Good teaching is directed toward the attainment of the most worthwhile objectives. Every teacher is faced with the necessity of making choices among a number of possible objectives. All things cannot be taught to all people. Good teaching is concerned with the selection of objectives which are the most important and most worthwhile. These objectives may be those which have to do with a long-term educational program, or with the more specific objectives to be attained in a particular course or even in a class period. Competence of the individual teacher in making wise choices is associated with an understanding of his total field of specialization and its relation to general education.

Good teaching recognizes the psychological principle that students learn through self-activity. Learning is not a passive process of absorption, but rather a process of reacting. Objectives can be achieved only by student exertion and application. The teacher, in reality, becomes the director of learning activities. The student listens, another time he looks, he makes a drawing, he visualizes, he remembers something, he sees a possible solution and tries it out, he searches for a reason, and with these activities and many others he makes progress toward his learning goals. If classes are conducted in such a way that little or no student activity takes place, then learning languishes.

Good teaching provides learning activities which are in fullest agreement with the type or types of learning desired. There are at least five types of learning. These are: sensory experience, memory, motor skills, problem-solving, and emotional. A teaching objective usually involves one or more of these types of learning. It becomes the teacher's responsibility to provide the kinds of learning activities which are involved in attaining the objective. In other words, the instructor teaches in a certain way if his objective is the development of problem-solving ability, another way if he is presenting information, and perhaps uses a different approach if he is working for motor skills. No one method of teaching works equally well in all situations. Teaching objectives and appropriate learning activities carry a concept which can be of value to every teacher.

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There is no one pattern of good teaching. Good teachers differ among themselves in personal characteristics and in their techniques and methods of instruction. Teaching is primarily a problem-solving situation. It includes competence in the determination of objectives, both ultimate and specific; an analysis of these objectives into a type or types of learning; and finally, the provision for learning activities by which the students attain these desired educational goals. The methods of a particular teacher, therefore, must be appropriate to his students, his subject matter, and himself. In all teaching situations, however, there are common elements of good teaching. These elements can be identified and, if recognized and understood, should contribute to a more effective solution of teaching problems.

Good teaching is directed toward the attainment of the most worthwhile objectives. Every teacher is faced with the necessity of making choices among a number of possible objectives. All things cannot be taught to all people. Good teaching is concerned with the selection of objectives which are the most important and most worthwhile. These objectives may be those which have to do with a long-term educational program, or with the more specific objectives to be attained in a particular course or even in a class period. Competence of the individual teacher in making wise choices is associated with an understanding of his total field of specialization and its relation to general education.

Good teaching recognizes the psychological principle that students learn through self-activity. Learning is not a passive process of absorption, but rather a process of reacting. Objectives can be achieved only by student exertion and application. The teacher, in reality, becomes the director of learning activities. The student listens, another time he looks, he makes a drawing, he visualizes, he remembers something, he sees a possible solution and tries it out, he searches for a reason, and with these activities and many others he makes progress toward his learning goals. If classes are conducted in such a way that little or no student activity takes place, then learning languishes.

Good teaching provides learning activities which are in fullest agreement with the type or types of learning desired. There are at least five types of learning. These are: sensory experience, memory, motor skills, problem-solving, and emotional. A teaching objective usually involves one or more of these types of learning. It becomes the teacher's responsibility to provide the kinds of learning activities which are involved in attaining the objective. In other words, the instructor teaches in a certain way if his objective is the development of problem-solving ability, another way if he is presenting information, and perhaps uses a different approach if he is working for motor skills. No one method of teaching works equally well in all situations. Teaching objectives and appropriate learning activities carry a concept which can be of value to every teacher.

Good teaching is unitary, rather than fragmentary. The more or less arbitrary division of course content into fifty four parts which can be presented in three fifty minute periods per week for one semester may result in learning by the student, but this learning may be made up of isolated information which is difficult to retain, and which the student is unable to use in a functional manner. Good teaching means unitary learning in which there is a constant development of relationships, functions, and ideas.

Good teaching provides for the release of the energy of students so that they can apply themselves fully. While there is some evidence that the amount of interest required for successful achievement in a special field is not so great as one might think, the college teacher has a definite responsibility to teach worthwhile materials in an interesting way. The teacher himself is the most important source of motivation. If the teacher is bored with the subject, expect the class to be; if the teacher is indifferent to the class, expect the class to be indifferent to the teacher; if the teacher is fascinated with the subject, expect the class to be; if the teacher is in a hurry to get on to something else, expect the class to be in a hurry to get on to something else. Each individual teacher needs to become a student of the motivation of human behavior, for an understanding in this area is definitely associated with successful teaching.

Good teaching provides for individual differences. Most specialized educational programs are selective in nature. While this selection undoubtedly cuts down the range of individual differences among students, groups are far from homogeneous. There will be differences in background, study habits, maturity, etc. It is possible that each student will approach learning differently. While specialized programs may require minimum standards of student proficiency, students may attain these standards in different ways. Good teaching, therefore, must take into account these differences which will inevitably exist among any group of students.

Good teaching is diagnostic and remedial. Sometimes learning seems to bog down. The class may run dead, or an individual student may experience difficulty. Little or no learning is taking place. Every teacher needs an understanding of the teaching and learning process which will enable him to identify the causative factors. Often the remedial work necessary to eliminate the block in learning can be provided by the teacher. Many universities have developed specialized remedial services. The teacher should be acquainted with the services offered and when the difficulty requires more time or more specialization than the teacher can provide, these services should be used.

Good teaching provides a physical and social environment which is favorable for learning. There is evidence that factors in the physical environment are related to progress in learning. The appearance of the room, arrangement of seating, cleanliness, temperature and humidity, all have an influence on learning. Not only are the physical factors important, but the social environment also contributes not only to the amount of learning but also to its quality. The business of the university classroom should represent a fine balance between cooperative en-

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deavor and individual enterprise. Classroom procedure should not resemble a contest in which the teacher is pitted against the students. The relation of student to student, and students to instructor is difficult to analyze and control. Yet, because of their importance, these relationships should serve as a challenge to each and every instructor.

In summary, it can be stated that teaching represents a complex, problem-solving situation. Information about and an understanding of the essential elements of good teaching will not lead with certainty to successful teaching. However, this background is useful as teachers meet the actual problems in the classroom, and should contribute to the improvement of instruction.

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CORRELATION OF PHARMACOGNOSY AND PHARMACOLOGY IN THE UNDERGRADUATE PHARMACY CURRICULUM

Egil Ramstad, Professor of Pharmacognosy
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Materia medica as taught in this country in the past was a course embracing present day's pharmacognosy and pharmacology, usually also including some aspects of physiology, posology, and toxicology. (1) This caused much confusion and delay in differentiating the fields of pharmacognosy and pharmacology (2). However, in the introduction of pharmacognosy and pharmacology as major courses of instruction this confusing state has largely disentangled; on the other hand, the separation of the scope of materia medica into these two courses has called forth an interest about the correlation of course content. The lack of training of the pharmacy student to think along physiological and biochemical lines is a regrettable obstacle for successful teaching of pharmacology on the level of a major subject.

The achievement of an adequate background in the chemistry of natural products and in basic biological sciences is essential in order to make possible the teaching of pharmacology on a high level. Any help that can be given to this end should be considered seriously. It is possible that the present pharmacognosy courses could be modified so as to contribute more amply to this end.

Since most of us are limited in our thinking about correlation of pharmacognosy and pharmacology by the traditional approach to pharmacognosy, and since that approach does not seem to offer much promise of correlation, let us try to establish some criteria of what <u>should</u> constitute the content of a pharmacognosy course. It is evident that only a small fraction of the sum of knowledge in any science can be imparted to the student, and one of the main problems the teacher of an applied science is faced with is not one of how-much-to-teach, but one of what-to-teach. We will therefore be forced to look for some guiding principles that can help us in selecting the material to be presented in the course. If we do not do so, the course may develop more or less into a cacophony of confusing, isolated facts of little or no constructive value. We may be trying to build a house without providing a proper foundation.

The specific objectives we have in mind when building a given course may vary with each teacher. But we probably can agree upon certain fundamental objectives. I think we must request of any course in an applied science that it should (1) provide for such information that will be useful to the student in solving problems, not only problems of today, but also of tomorrow. The more the knowledge can fulfill this purpose, the more desirable it will be. (2) The teaching of principles should be preferred to communication of isolated facts. Facts are readily forgotten and can be found in handbooks; understanding is more difficult to acquire, but, when obtained, becomes an integral part of the individual. Only then can the course really be meaningful to the student.

CORRELATION OF PHARMACOGNOSY AND PHARMACOLOGY

IN THE UNDERGRADUATE PHARMACY CURRICULUM

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Pharmacognosy cannot be looked upon as an isolated section of the pharmacy curriculum with no connection to other pharmaceutical studies. The pharmacognosy course for undergraduates should therefore be outlined in such a way that:

(1) The information to be presented serves to accomplish the role consigned to pharmacognosy as a building stone in the pharmaceutical education program so as to help qualify the pharmacy student for his future profession;

(2) The course accomplishes the objectives of pharmacognosy as a science;

(3) Pharmacognosy, being a biological science like pharmacology, and preceding pharmacology in the pharmaceutical curriculum, aids in building a background in biological sciences that will be desirable for the succeeding pharmacology courses.

In my opinion, all these objectives can largely be accomplished by revising and modernizing the content of the pharmacognosy courses.

How does the traditional approach to pharmacognosy courses that is commonly taken today satisfy these requirements? Pharmacognosy as a science dates back to the beginning of the 19th century. Although the chemical knowledge of natural products was constantly increasing during the century, the natural drugs in their crude form or in the form of partly purified galenical preparations dominated in therapy. Under these conditions, the pharmacists actually had to collect drugs, preserve and convert them to galenicals. There was no food and drug administration to protect the buyer. The pharmacist had to identify imported drugs and judge their quality. Because of these conditions, a knowledge of flora, of drug morphology and in some instances also of drug anatomy, was important, or, perhaps essential in the practice of pharmacy. However, science and industry began to progress rapidly in the 19th century and progressed with accelerated speed during this 20th century. The 19th century was the century of industrialization, of the springing up of metropolitan areas, of technical and commercial expansions. More and more, pharmacists discontinued collecting their own drugs; reliable pharmaceutical manufacturers gradually took over the extraction of crude drugs, and today, if the crude material is needed by the pharmacist, he can purchase the standardized product from reliable wholesale sources which have made a specialty of handling such products. As the active constituents of the crude drugs were isolated and made available, a gradual decline occurred in the pharmacist's dealing with the crude material as such. With the rapid development of chemistry, biochemistry, physiology, and pharmacology, the pure product from crude natural drugs, however, did not decrease in importance. On the contrary, discovery upon discovery brought them more and more into the focus of interest in therapy.

Illogical as it may sound, these developments had but very little influence upon the set-up of the pharmacognosy courses. A taxonomical classification of crude drugs remained the standard approach. The teaching pf plant family characteristics and botanical origins, which involved the memorization of hundreds of Latin names and geographic origins, continued. Plant descriptions, morphological, and anatomical studies of crude products also continued to be essential features of the courses.

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Some schools still lay such weight on drug histological studies that it has been maintained that they are "trying to make expert plant anatomists out of the undergraduate pharmacognosy students". (3)

A feeling that the contents of pharmacognosy courses are often impertinent and obsolete prompted The Pharmaceutical Survey, two years ago, to state that "Pharmacognosy as taught in many schools of pharmacy is now in need of drastic revision".

There is another approach to pharmacognosy by which the objectives stated previously can better be accomplished, that is by a chemical or biochemical-physiological approach.

It is recognized that the particular pharmacological actions of natural products derive their origin from definite chemical entities elaborated by the living cells. The interest of the pharmacist as well as of the pharmacologist will therefore logically center about the active principle of crude natural products. The active constituents also constitute the center of the pharmacognosist's interest in the drug since the existence of this chemical entity is the very reason why the drug is included in pharmacognosy. In fact, this is so evident that, as far back as half a century ago, Tschirch, the grand old man of pharmacognosy, used a chemical system of classifying plant and animal drugs in his outstanding handbook of pharmacognosy.(4) Leroy D. Edwards (3) claimed 11 years ago, a chemical classification of natural drugs to be the most suitable one for undergraduate study. I know it works, for I was using that system myself in undergraduate pharmacognosy courses in 1941. The chemical treatment of natural drug products should therefore be given much more emphasis than is given in schools today. I do not think it advisable nor feasible to take up an individual treatment of all constituents in natural drugs in the undergraduate courses. However, the student should acquire sufficient familiarity with the types of compounds to be able to judge correctly about their physical and chemical properties bearing upon solubility, stability, and incompatibility, Key compounds, or compounds whose detailed chemistry may be particularly important, should be treated more in detail. The effect of aging and physical factors, decomposition, racemization, etc. cannot fail to be of interest to the pharmacognosist nor to the pharmacologist. The chemistry also furnishes a clue to the understanding of methods used in the extraction of crude drugs and in the preparation of pure compounds. It will also help in understanding the behavior of galenical preparations. The student should be led to understand why cold storage of sera is needed, why penicillin loses its activity in aqueous solution, why digitalis leaves must be stored under anhydrous conditions, why insulin must be given parenterally, and so forth.

The pharmacognosist as a scientist studies the drugs of natural origin from every point of view. As it has been stated, it will be logical in an undergraduate course to direct the attention more largely towards the active constituents. These constituents, however, are not only of interest because of their effect on the animal body. They have a function in the body of the producing organism too. An alkaloid, a glycoside, a vitamin should also be considered from the point of view of its relation in the producing organism, as it has been pointed out repeatedly. (5) (6). In other words, they should be looked upon as parts of the living system, as functional parts of the cells. A fermentation product, as for instance citric acid or glycerol, will acquire a different significance for the

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student when looked at from the standpoint of cell metabolism. We are interested in the mechanisms of biosyntheses of the drug compounds both because we want a better understanding of the workings of the living organisms, and because we are directly interested in the problems of how to affect the production, say of penicillin or vitamins, from precursors. The vitamins are of no less importance in the enzyme constitution of the plant than in the enzyme constitution of animals. Enzymes and enzyme regulatory mechanisms have implications in drug production as well as in drug actions and drug transformations in the animal body, or in the effects of drugs on microbes. Antibiotic production by microbes and antibody formation by man are but two faces of the general struggle for survival. But both phenomena should be understood. Problems related to the influence of environmental factors such as temperature, pH, mineral, and organic nutrients on the drug producing organism should be of value for the understanding of biological processes in general, and even a discussion of the value of various plant strains for the production of drugs (e.g. penicillin, ergotamine) should lay a basis for the understanding of mutation in the phenomenon of drug fastness.

The pharmacologist does not wholly content himself with describing the physiological responses to drugs. He, too, sees the ultimate goal to be able to explain the action as the effects of the drugs on the chemical processes occurring in the cells. In the future we shall know more about those ultimate mechanisms of drug action. The pharmacologist, in order to make himself understood when explaining the cellular mechanism of drug action, needs an audience that is familiar with biochemical thinking. Whether this is acquired by study of animal or plant does matter little. Let us not forget that the biochemical design of plant and animal cells shows a close similarity, a fact which apparently was realized decades ago by Claude Bernard when he stated that "Animals and plants live identically, but function differently". Although there is this difference in functioning of animals and plants, the inclusion of plant physiological problems related to drug production in a pharmacognosy course should develop in the student the ability and the habit of thinking more along biochemical and physiological lines.

There has been raised question about the necessity of pharmacognosy as a background for the practicing of pharmacy. It seems likely that fewer will consider pharmacognosy indispensable for the pharmacist in the future, unless a recasting of the pharmacognosy course can make it pertinent and adapted to the needs and problems in handling of drugs by today's practitioners of pharmacy. A reduction of the taxonomical, morphological, and anatomical emphasis in pharmacognosy undergraduate courses and modernizing it by taking a more chemical, biochemical, and physiological approach to pharmacognosy, should change it into a useful and important course that should broaden the outlook of the student.

Under the present four-year pharmacy training program the pharmacy student is likely to have considerable background inadequacies in biology, a fact that will tend to make it difficult for the

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pharmacology teacher to give his course on a level it deserves, and difficult for the student to profit fully from pharmacology as a major course. Pharmacognosy as a biological science can here be of considerable help, if it is given more liberally the character of a formative biological subject than it is at the present time. An approach to pharmacognosy as the one indicated will not only make this science more useful as a pharmaceutical subject, it will be profitable to pharmacognosy itself, and it will help greatly in providing foundation for the comprehension of the influence of drugs on cellular physiology of normal and abnormal tissues.

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GENERAL DISCUSSION AND SUMMARY OF THE FINDINGS RELATIVE TO THE UNDERGRADUATE COURSES

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Pharmacy, as is true of other fields of service in the care and cure of the sick--and may I include the maintenance and promotion of the state of health--cannot now be considered a "private enterprise". A trend that had become manifest before the advent of the sulfonamides--that of the preparation of medicinals for retail distribution by methods of large-scale manufacture--became steeper as the relative efficacy and safety of these and the subsequent antibiotics became known. Where the medicinals previously employed were largely directed toward treating symptoms and easing pain, now true chemotherapeutic agents were more often employed and by their specific action shortened the period of illness. These chemotherapeutic agents were products of organic synthesis or large-scale culture which required exact physical and chemical conditions for their production, and effective competition by the individual pharmacist was not possible.

Secondly, the trends toward medical care for all of our peoples, irrespective of financial status, and toward medical care in a hospital rather than in the home have contributed to make pharmacy even less a private enterprise.

Consequently, the practice of pharmacy by the pharmacist as we have known it must change. No, it has changed. It is not now mainly the preparation and dispensing of drugs by the individual pharmacist. As a result of this change in the practice of pharmacy, pharmaceutical education must make adjustments. Such a challenge is not to be feared. It presents an opportunity.

The modern pharmacist is a member of the public health team, the drug specialist in this team. In this role knowledge of pharmacology serves him well.

As Dr. Francke pointed out, hospital pharmacists have an opportunity to make use of pharmacological knowledge constantly. In hospital formulary work, in large and small scale manufacture, in service to the staff physicians, to give service knowledge of pharmacological principles are of utmost importance. Good service is appreciated and brings of itself professional standing. Similar opportunities are available to pharmacists in the professional stores, to the general pharmacist serving the small community, to the research pharmacist in the manufacturing house, etc. To take his place as a member of the health team, increased professional training is needed to make the pharmacist the drug specialist, and pharmacology is the chief discipline in this extra training.

The objectives of pharmacological training as brought to our attention by Dr. Maher are to make the pharmacist a man of wide and accurate knowledge of the physical and chemical properties of drugs and of their effects on the body. Let him realize that drugs are used both for health and against disease. Let him have the confidence that general and specific knowledge brings, and the ability to discard the old ideas and accept the new. An able education of first hand knowledge (laboratory)

GENERAL DISCUSSION AND SUMMARY OF THE

FINDINGS RELATIVE TO THE UNDERGRADUATE COURSES

Nellie P. Watts
New England College of Pharmacy
Boston, Massachusetts

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and continued education (library) will do much to make the pharmacist ever young. With undergraduate pharmacy students it is to be expected that approximately 90% of them will become retail pharmacists and training for a broad outlook, with appreciation of the place of drugs in the total health field and the place of pharmacology within the field of pharmaceutical education, is the goal.

Dr. Edwards pointed out that pharmacology is a synthetic science. It uses freely from the disciplines of mathematics, chemistry, physics, and biology. Its uniqueness rests in the use of other sciences to obtain knowledge about drugs. Since it borrows from these fields of science, it is necessary that much understanding of these sciences be acquired before the study of pharmacology is begun.

Generally, biological instruction in the schools of pharmacy is at a lower level than is chemical. This is true with respect to the number of courses available and the level of instruction in these courses. More and better laboratory instruction is needed.

Dr. Edwards recommended as minimum prerequisites in the biological sciences for undergraduate pharmacology standard university courses, with laboratory, in

General biology
Vertebrate anatomy - gross and microscopic
Physiology
Pathology (elective)

In addition to these biological sciences, it was recommended that prior to pharmacology instruction, chemistry courses (through organic and bio-), physics, mathematics, and microbiology be completed. We heartily agree.

Dr. Deno's report, based on his study of the colleges shows that instruction in many colleges must be raised to meet these requirements. The quality of instruction and the quantity are both below that recommended. Pharmacology requirements are no more than half met.

Dr. Holck, in his discussion of the didactic course in pharmacology, recommended the use of modern textbooks of wide coverage, supplemented by reading of the journals. He proposes that the student shall acquire, in addition to knowledge of general principles and specific facts, a rich vocabulary of the sciences and ability to apply his knowledge.

The aim of laboratory instruction in undergraduate pharmacology is, as stated by Dr. Swinyard, "to explain, expand, and dramatize the work covered in lecture". He recommended, therefore, that the laboratory instruction be correlated with the lecture, that the experiments be simple, and selected to establish principles, that the drugs employed bear a relationship to their importance and current use, and that discussion of the experiment and correlation of results follow the laboratory period. A critically selected number of motion pictures are of value. In no case, however, is their use to replace that of the simple laboratory experiment. Library study should be used in conjunction with the various experiments. Regarding the student's notebooks the members of the conferences are not in agreement. Regarding the laboratory manual, however, we are in agreement that the preparation of one's own is to be preferred to the use of those commercially available. Thus, one can make use of what is available locally and change the content of the manual readily.

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The laboratory is the core of pharmacology teaching. Much time and effort should be expended in its planning, as pointed out by Dr. Nelson. Too, it should be planned with the cooperation of the pharmacologist who is to teach in it. Consideration should be given to the size of the experimental group, the class or section size--Dr. Nelson prefers a section of 24 students and a group of 4 students to a table--and the services required. In the laboratory, elaborateness is not to be desired but workability and efficiency are. A place for demonstrations should be provided, but this place should not be often used--student experiments make for better teaching. The individual faculty laboratory-offices, the research laboratory, the workshop, stockroom and animal room should be located convenient to the student laboratory. Local conditions determine how large the animal room should be and whether an incinerator or other means of animal disposal are required.

In some instances the pharmacy students are taught pharmacology by the faculty of a department of pharmacology of a medical school or of a university. In many instances this has been unsatisfactory because the level of instruction has been inferior to that given other pharmacology students, the course has been abbreviated, and it has been given without enthusiasm. Special acclaim is here given to Dr. E. G. Gross of the State University of Iowa. He serves well all students who come to him. A large department of pharmacology, in many instances, may serve pharmacy students better than an individual teacher of the pharmacy school faculty. Such a department may have a large staff and be able to offer specialists in the various fields of pharmacology, and may have hospital connections with the wealth of illustrative material such a connection brings. Pharmacy students come to pharmacology as seniors, or in some instances as juniors, and are better prepared than many pharmacology students to understand structure-action relationships. Their instruction should cover a wider range of drugs than that of a physician, dentist, or veterinarian since the pharmacist is to serve all these professions.

Dr. Holck has spoken to us recently on the desirable qualifications of instructors. In no case should their basic training be less than that of a Ph.D. major in pharmacology. They should be experienced as pharmacologists and as teachers. They should be growing, active members of their profession doing research, reading, conferring with others, visiting other laboratories. The teacher should bring enthusiasm to the class, integrate pharmacology in the health sciences and in the pharmacy curriculum.

The teacher should remember that his place of service extends beyond the classroom and laboratory in which he works. He also serves a community; he has citizenship duties; and with his students his role does not cease with the final examination. The teacher's role is to serve.

We have been privileged this morning to have Dr. Alexander, Professor of Education of Purdue University, speak to us. We are appreciative of this. Yes, we must labor on for better training of the student before he comes to us for pharmacology--better laboratories with better equipment, better training for the faculty, and lighter teaching loads in order that we may serve more intensively. However, the good teacher is resourceful and provides a steady, rich background in which the student best learns. The time to give more and better pharmacology instruction in schools of pharmacy is now. We are to provide good teaching at the same time as we are obtaining better conditions. The results may be better than one could expect from the raw material.

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THE MECHANISM OF DRUG ACTION

Kenneth P. DuBois
Department of Pharmacology, University of Chicago
Chicago, Illinois

The mechanism of drug action is a subject which is currently receiving an increasing amount of attention but nevertheless may be considered as being in an early stage of development. While pharmacology as a science has no clear-cut boundaries, it has in the past largely centered around physiological measurements of the actions of drugs on the intact animal and on isolated organs. It has also emphasized extraction and purification of medicinal compounds of plant and animal origin and the development of synthetic compounds with useful therapeutic properties.

The physiological approach to pharmacology is of primary importance because defining the principal actions of a drug on the intact animal and on isolated organs is an essential step which should precede its clinical use. Ascertaining the toxic side reactions, searching for injurious effects by the drug through pathological studies and determining the fate of the compound in animal tissues have become standard prerequisites for the introduction of any new substance into practical use. This phase of pharmacology is thus indispensable as a primary consideration in research, teaching, and practical usage of chemical agents therapeutically.

The mechanism of drug action might be considered, from a practical standpoint, to be a dispensable phase of pharmacology. However, as I shall attempt to illustrate, studies on the mechanism of drug action can in itself be employed as a means of developing new drugs, as a procedure for arriving at a scientific approach to the treatment of diseases and antidoting poisons.

For pharmacology to grow as a science we must devote attention to the fundamental aspects of drug action. The distribution of drugs in tissues must be understood, the permeability of cells to drugs and the effects of drugs on permeability must be elucidated and alterations in cell function produced by drugs must be interpreted in terms of cellular biochemistry. All of these problems constitute the foundations for a science of chemotherapy and drug action. At the present time we are only beginning to probe the nature of drug action. It seems that our best approach to the problems of drug action is to obtain a clear picture of the make-up of living cells so that we can reconstruct in exact chemical terms the series of events which we call cell metabolism. The knowledge gained by such an approach should enable us to appreciate the actions of drugs on cell metabolism and gain a secure base from which to conduct future research on the development of therapeutic agents.

The modern concept of the action of drugs has as its basis the idea that all therapeutic agents produce their effects through (a) chemical interaction with some cellular constituent or (b) a physical action on cell surfaces. The majority of drugs and poisons appear to act by entering into or interfering with one or more biochemical events which occur in cells. Thus, by inhibiting or stimulating various reactions or by correcting a deficiency in some essential metabolite normal function is

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resumed in cells injured by disease. According to this general viewpoint, poisons block the sequence of biochemical events in cells and thus prevent the normal cellular functions from proceeding.

The extremely small doses of many drugs and poisons which will alter the physiological functions of cells indicates specificity on the part of the drug in its action on cellular constituents. The general term protoplasmic poison which has so often been applied to toxic agents is now obsolete for it suggests a general and non-specific reactivity seldom observed among drugs and poisons.

Within recent years increasing attention has been given to the possibility that many drugs produce their effects by functioning as activators or inhibitors of enzymatic reactions. Such an interpretation necessarily implies that the diseases for which the drugs are intended are due to an inbalance in the enzymatic reactions in cells. From this idea it follows that various diseases constitutes a disturbance in cellular biochemistry. Thus, for example, cardiac decompensation would be considered to be due to a biochemical abnormality in the metabolism of heart muscle and the cardiac glycosides correct this biochemical deficiency or injury.

Progress in the field of the mechanism of drug action necessarily depends upon progress in the field of cellular biochemistry. Most of our present knowledge of cellular metabolism has been obtained during the past twenty years as a result of improved methods for isolating enzymes and methods for measuring enzyme activity. As a result of this progress investigations on cellular metabolism have gradually assumed a more quantitative aspect.

The first serious consideration of the mechanism by which drugs act can be attributed to the work of Ehrlich in the early part of this century. During his studies on chemotherapy he suggested that drugs exert their effects on parasites by direct chemical combination of the drug with the parasite. He thus stimulated <u>in vitro</u> studies of the actions of drugs on cells. In 1914 Simon and Wood put forth the idea that since intracellular metabolism is dependent upon the action of enzymes, the deleterious effects of poisons may be due to an interference with the activity of these cellular components and that the cell dies not necessarily because it has been poisoned but rather because a sufficient number of cellular enzymes have been thrown out of action to render the cell incapable of performing the functions vital to life. The suggestions of Ehrlich and of Simon and Wood were purely speculative at that time but since then have been given an experimental basis by many investigators.

Investigations by Warburg and Keilin in 1913 to 1929 included studies on the effect of narcotics and poisons on the respiration of intact organisms and provided a much needed link between isolated enzymes and cellular metabolism. They found that certain compounds such as urethane and alcohols inhibited the respiration of intact cells. When the same narcotics were added to cell-free enzyme preparations the inhibitory effect was less than on the intact animal. Warburg suggested that this was due at least in part to the selective action of the cell membrane which transmitted lipoid-soluble substances rapidly to the interior of the cell. Cyanide on the other hand inhibited respiration at a far lower concentration than narcotics and had a highly specific effect on oxygen

uptake. Warburg interpreted this as indicating the presence in cells of a cyanide-sensitive enzyme system which is now known as cytochrome oxidase.

Since 1930 rapid progress has been made in elucidation of the enzymatic reactions involved in the energy-yielding processes in the cell. In addition quantitative methods for estimating enzyme activity have been developed. In this connection the introduction of the use of tissue homogenates by Potter and Elvehjem in 1936 was a particularly valuable contribution because it has been possible to carry out quantitative assays on tissues taken from animals treated with drugs by using tissue homogenates. It is therefore no longer necessary to rely solely on in vitro tests which are often times misleading insofar as interpretation of events occurring in the intact animal are concerned.

The general procedure employed in our laboratory for the study of drug action may be illustrated by the results of investigations on cholinergic drugs. Our interest in this subject began in 1947 when we initiated pharmacological research on a new insecticide called hexaethyl tetraphosphate. This material had been introduced and successfully employed for the control of plant aphids in Germany. It was reported to have a nicotine-like action but no further information on its pharmacological effects was available.

During toxicity studies on HETP we observed that animals poisoned with this compound showed symptoms typical of those produced by parasympathomimetic drugs like DFP, neostigmine and physostigmine. Muscular twitching, tonic and tonic-clonic convulsions, involuntary defecation, micturition and salivation were noted. These symptoms are referrable to an increased activity of the parasympathetic nerves, somatic motor nerves and the central nervous system. It, therefore, seemed likely that the chemical mediator for the nerves involved was elevated through an inhibition of cholinesterase which normally causes rapid hydrolytic disposal of acetyl choline. Tests on the effect of HETP were then conducted and we observed that this compound was a potent inhibitor of the cholinesterase of insects and mammalian tissues. The insecticidal action of this compound as well as its toxicity to mammals appeared to be explainable on the basis of cholinesterase inhibition with the consequent increase in acetyl choline.

However, it is not safe to assume that in vitro inhibitory effects of drugs on enzyme systems also occur in vivo. The in vitro tests give an indication of the possible effects in the intact animal but final proof of the mechanism of action requires tests on tissues taken from animals treated with the drug wherever possible. In the case of cholinesterase we devised a method for assaying the activity of animal tissues. The procedure involved the use of homogenates of various tissues and the quantity of acetyl choline hydrolyzed per unit of tissue in 30 minutes was measured manometrically making use of the well-known procedure in which the acetic acid liberated from acetyl choline was allowed to react with bicarbonate in a closed system and the carbon dioxide liberated was recorded as an index of cholinesterase activity. In devising this method we set up test conditions which would allow accurate assays of the enzyme concentration in the tissue. The procedure has been applicable throughout our investigations during the past five years not only for animal tissues

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but also for studies on insect tissue of widely varying cholinesterase activity. Selection or development of an assay procedure which is applicable to all phases of a research problem is of primary importance in initiating work on the mechanism of drug action, for with a method which does not need to be modified from time to time it is possible to compare data obtained throughout the entire period of experimentation.

To prove that HETP inhibits cholinesterase in vivo as well as in vitro lethal and sublethal doses of the compound were administered to rats and cholinesterase measurements were performed at the time of death or at 20 minutes after administration of sublethal doses. These assays demonstrated that HETP markedly inhibited the cholinesterase activity of several tissues in vivo. In these assays brain, submaxillary gland, skeletal muscle, and serum were studied since the symptoms produced by the compound indicated that the activity of the central nervous system and peripheral tissues was inhibited. In drug action studies it is always necessary to give particular attention to the tissues which are affected by a drug in the intact animal. The fact that HETP produced an inhibitory effect on the cholinesterase activity of both central and peripheral cholinesterase indicated that the compound gains access to all tissues of the body.

From the standpoint of accidental poisoning by this insecticide it was important to determine whether the effects of HETP on cholinesterase were reversible. For this type of study on any drug the pharmacological approach involving administration of a sublethal dose of the drug followed by assays on tissues of treated animals at various intervals seems preferable to any other procedure. Thus with HETP we observed that the inhibitory effect was reversible within a few days after administration. This finding would be anticipated in view of the reversible miosis and the rapid recovery of animals which receive a sublethal dose of the compound. In the cases of accidental poisoning by this compound in man rapid reversibility of the effect has been noted in agreement with the results of our enzyme tests. On the basis of in vitro tests alone other investigators thought that this compound produced an irreversible inhibition of cholinesterase because dialysis failed to restore the enzyme activity. It is thus clear that we must perform assays on the tissues of treated animals to determine the duration of enzyme inhibition by drugs since factors not operative in vitro apparently come into action to influence the duration of drug enzyme combinations. If correlations between the duration of symptoms or pharmacological actions and enzyme inhibitions are sought it is necessary to show that the duration of inhibition correlates with the duration of symptoms.

TEPP.----During investigations on HETP we suspected that rapid hydrolysis took place to yield an active product and that this hydrolysis product had a potent cholinergic action. Several possible breakdown products were therefore obtained and tested for anticholinesterase activity. Among them was tetraethyl pyrophosphate which proved toxic enough to be considered as the active hydrolysis product formed from HETP. Subsequent work has substantiated our initial deduction that TEPP is the active agent in HETP.

Our work on this compound was carried out in a manner similar to the studies with HETP. The compound was administered to animals and the symptoms were closely observed, the rapid onset of action was noted and

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Our work on this compound was carried out in a manner similar to the studies with HETP. The compound was administered to animals and the symptoms were closely observed, the rapid onset of action was noted and

reversibility of the pharmacological effects was demonstrated. All of the tests on the intact animal were suggestive of a mechanism of action involving inhibition of cholinesterase with the consequent accumulation of acetyl choline. Tests on the effect of this compound on the cholinesterase activity of rat brain showed that the compound produced 50% inhibition of cholinesterase at a final M conc. of 4×10^{-9} and was therefore one of the most active cholinesterase inhibitors known. Assays were then performed on this enzyme on the tissues of poisoned animals and it was found that the cholinesterase activity of all tissues was markedly depressed after administration of lethal and sublethal doses. There was a correlation between the dose of TEPP and the extent of the inhibitory effect on various tissues. It was always observed that lethal doses produced more than 75% inhibition of the enzyme activity. The inhibitory effectwas reversible after sublethal doses in agreement with the reversibility of the symptoms produced by the compound. Insect cholinesterase was also markedly inhibited by the drug. Soon after these studies were made tetraethyl pyrophosphate came into use as an insecticide. It also proved useful as a substitute for neostigmine in the treatment of myasthenia junction and thus relieves the muscular weakness which is apparently due to an insufficient quantity of acetyl choline.

Shortly after the introduction of TEPP into use as an insecticide another organic phosphate, called parathion, was introduced into this country from Germany. With previous experience in studies on TEPP and related compounds it was possible to begin to associate pharmacological activity with chemical structure. By following the same general type of approach with this new compound we were able to demonstrate that it also was an extremely effective anticholinesterase agent <u>in vitro</u> and in the intact animal. In all respects parathion resembled TEPP, i.e., it gained access to and inhibited the cholinesterase activity of all tissues, produced typical cholinergic effects, was antagonized by atropine. There was one difference in that the effects of parathion persisted for a longer period of time than those produced by TEPP. This longer duration of action is probably related to the greater stability of this compound toward hydrolysis. From a practical standpoint this has resulted in a number of cases of poisoning from continued exposure.

OMPA-----Our investigations as well as those of a number of others on a large number of alkyl phosphates have shown that all of the compounds in this group exhibit similar pharmacological properties. The particular alkyl group influences the degree of effectiveness but does not greatly alter the qualitative effects. Thus, all of the alkyl phosphates studied have been shown to exert a rather pronounced inhibitory action on the cholinesterase activity of brain tissue and substitution of one alkyl group by another alkyl or aryl group does not significantly decrease this action. The value of the alkyl phosphates as insecticides is not diminished by this property but the central action of these compounds constitutes an undesirable effect insofar as therapeutic uses are concerned.

We, therefore, continued investigations on the mechanism of action of organic phosphorus-containing compounds in an effort to find substances which lacked the central stimulatory effect of the alkyl substituted phosphates. We reasoned that in order to find such compounds among the organic phosphates the search should be directed toward substances which did not contain the alkyl or aryl phosphate linkage. In this connection

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we undertook studies on octamethyl pyrophosphonamide.

This compound was among the organic phosphate series which was prepared by Schradeer in Germany and it has recently attracted attention because of its unusual insecticidal properties. It differs from TEPP and many other alkyl phosphates in that it is stable in aqueous solutions and has been defined as a systemic plant insecticide because it is taken up by plants and retained by them for several weeks in a toxic form.

A study of the toxicity and anticholinesterase action of this compound was undertaken to ascertain whether it exerted a cholinergic action in mammals. Injection of the compound into mammals showed that it produces cholinergic actions in low doses. However, in vitro tests showed that this compound was ineffective as a cholinesterase inhibitor, On the basis of in vitro tests alone OMPA would have been eliminated from further consideration as a cholinesterase inhibitor. However, from observations on the symptoms and toxicity of the compound we suspected that it inhibited cholinesterase in vivo and therefore measured the cholinesterase activity of tissues taken from rats treated with lethal and sublethal doses. It was found that the cholinesterase activity of all peripheral tissues was markedly inhibited by OMPA. However, in contrast to all other phosphates previously studied there was no inhibition of brain cholinesterase. This pronounced difference between the action of OMPA on the cholinesterase activity of brain and peripheral tissues can probably be attributed to inability of the drug to gain access to the CNS. The absence of an effect by OMPA on brain cholinesterase in vitro is consistent with the absence of symptoms referrable to stimulation of the central nervous system. Measurements of the duration of the inhibitory effect of OMPA on cholinesterase showed that the effect persisted for several days.

During the course of investigations on OMPA several observations led us to suspect that the compound was converted by the tissues of animals into an active anticholinesterase agent. The weak action of OMPA in vitro in contrast to its inhibitory effect in vivo was evidence in support of this possibility. The delayed onset of action of OMPA which is uncommon among cholinergic drugs also suggested that the compound undergoes an alteration in chemical structure before exerting its cholinergic effects. By incubating OMPA with liver slices we were able to demonstrate that it was converted to an active cholinesterase inhibitor. Slices of brain, kidney, and muscle were unable to carry out this conversion.

The selective action of OMPA on peripheral cholinesterase, its stability in aqueous solutions, and its relatively long duration of action are properties which have been desired for therapeutic application of the organic phosphorus-containing compounds. It appeared that OMPA had the properties which would make it desirable as a therapeutic agent. Clinical trials were therefore initiated with this compound at the University of Chicago by Dr. Rider and his associates. OMPA was administered as a 1% aqueous solution twice a day at intervals of approximately 12 hours. The course of therapy was regulated by the clinical response and by the depressant effect of OMPA upon the serum and red cell cholinesterase. The results of these tests showed that myasthenia gravis patients who respond to neostigmine can be treated with OMPA by administering two oral doses per day of from 9.5 to 18 mgm. of OMPA/dose. OMPA constitutes an improved method of therapy for this disease because muscular strength is greater and is maintained more evenly than with neostigmine. In addition

the stability of OMPA in aqueous solutions presents an advantage over TEPP.

The results of these investigations have shown the applicability of enzyme methods to the development of therapeutic agents. After an indication of the mechanism of action is obtained it is then possible to proceed with tests on variations in structure and activity. In addition it is possible to obtain information of practical value in connection with toxicological aspects of these agents. Perhaps these comments illustrate the objectives of drug action studies and some of the things which can be accomplished using this approach to the development of new drugs.

Other such studies could have been used as examples of the fruitfulness of this approach to pharmacology. Among these is the development of dithio mercaptol (BAL) by Peters. The usefulness of this agent for the treatment of mercury and arsenic poisoning came as a result of the tests performed by Peters on the action of lewisite on SH enzymes.

Recent studies on Be poisoning have shown that this metal inhibits phosphatase activated by Ca and Mg and causes a serious disruption of the synthesis of phosphorus-containing compounds.

The advancements in cellular biochemistry are extremely valuable in studying drug action and enables pharmacologists to give back useful information to biochemists in the way of specific inhibitors for blocking various reactions. In this connection the use of CN has exceeded all other inhibitors and it is a standard agent in determining whether organisms contain CN-sensitive enzyme systems. Be will be useful for blocking the action of certain phosphatases.

Continued studies on the mechanism of action of drugs offers the possibility of gaining a precise understanding of the manner in which they act and in addition if the mechanism of a drug's action is understood, we will be better able to understand the basic defects in various diseases.

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VALUE OF BIOCHEMISTRY TO PHARMACOLOGY

R. C. Corley
Department of Chemistry, Purdue University
West Lafayette, Indiana

Pharmacology and biochemistry share a large area of science and are mutually complementary and helpful in other areas. One of the fundamental fields of biochemistry is the elucidation of the chemical reactions that make up metabolism. These reactions are largely mediated by enzymes and systems of enzymes. Pharmacology throws light on and provides tools for studies of problems of metabolism. The objective of biochemical collaboration with pharmacology is to discover in metabolism critical sequences that chemical agents may modify by preventing, diverting, diminishing, or augmenting certain essential steps.

Biochemical techniques are of constant application in the study of the extent and mode of action of drugs. Analyses of tissues, blood and urine and other fluids and intestinal contents are frequently necessary to answer questions concerning absorption and excretion of the drug and of induced chemical effects. Procedures for the manipulation and study of enzymes and tissue preparations, slices and homogenates, are of frequent use.

Knowledge of metabolism has made possible already, and progress in understanding of biochemical phenomena will make increasingly possible, not only explanation of the action of many drugs, of the development of resistance to drugs, and of the fate of drugs in living tissue, but also predictions as to the effect of untried substances and consequently the design of new and improved drugs and the planned modification of the effects of drugs and toxic agents.

The explanation for the mechanism of action of a drug is often to be found in its influence on one (or more) of the participants in the sequence of chemical reactions in metabolism. The drug may combine with the substance involved to give a derivative incapable of functioning normally, either because of changed reactivity or because a combining group necessary for further reaction is occupied. Reactions of iodoacetate, mustard gas and lachrymators with the thiol group of certain enzymes exemplify the first type in which the extent of inhibition varies with the amount of the drug. The interference of the sulfa drugs with the utilization of para-amino benzoic acid and folic acid, of dicoumarol with the vitamins K, and of pyrithiamine with thiamine are reasonably explained as examples of the second type. In accord with this view the relationships appear to be competitive, the extent of inhibition being related to the relative amounts of the inhibitor and of the metabolite or substrate.

Explanation of drug resistance may be based on related concepts. There may be increased production of the essential metabolite or drug antagonist, as para aminobenzoic acid in some microorganisms showing acquired resistance to sulfa drugs. There may be the development of nonsensitive alternative procedures for the synthesis or degradation of the essential material. Production of glycerol rather than ethanol in yeasts in the presence of sodium bisulfite is an analogous situation. There

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might result an increased capacity for detoxication or chemical alteration in general. Information concerning the fate of drugs in the organisms is increasing and should be accelerated, the better to understand these various problems.

The design of new drugs by modification of known ones is facilitated by knowledge of the biochemical bases of the actions. The design of a drug to possess a new effect logically starts from a consideration of chemical reactions relating to the function, alteration of which is sought. Examples of these approaches are to be found in the production of antithyroid, antihistaminic and antimalarial drugs. The new rodenticide Warfarin inducing fatal hemorrhage is patterned after dicoumarol, a competitive antagonist of vitamin K required for the production of prothrombin necessary for clotting of the blood.

Viruses affecting plants have been shown to be or characteristically to contain nucleoproteins. As replication may be expected to involve synthesis of the constituents of nucleoproteins, interference in the synthesis of any of the necessary building units, such as the purines, might interfere with spread of a virus infection. In accord with this view it has been reported that guanazolo, a triazolopyrimidine patterned after guanine, decreased the incidence and severity of infection with a certain plant virus when applied to leaves of a susceptible plant or to the soil in which the latter was growing. Guanazolo had previously been reported to inhibit the growth of a plant tumor.

Problems arise concerning the modification of the action of drugs and toxic agents. B. A. L., 1,2-dimercapto-propanol was designed to prevent or ameliorate the effects of vesicant drugs such as mustard gas, by displacing such drugs from combination with enzymes, as hexokinase. Aminopterin a relative of folic acid has been suggested and used in the treatment of leucemia on the basis of possible interference with purine and pyrimidine metabolism and therefore with nucleoprotein metabolism which is more active during rapid tissue proliferation. The toxicity of aminopterin is a deterrent to its use but more recently it has been suggested that folinic acid given at the same time, may counteract general tissue toxicity as it may be the enzymatically active form or is closer to it than folic acid itself. The possibility of finding agents which under controlled conditions will selectively repress tumors and cancerous tissues while leaving other tissues relatively or entirely unaffected is a challenge to the investigator. The diabetogenic action of alloxan may be taken as analogous.

Consideration relating to the reactions in metabolism may thus offer clues or provide guide posts for further work. As our knowledge is still fragmentary and will probably remain so for a long time, only careful study of the actual response of living organisms, the province of pharmacology and toxicology, will make possible therapeutic applications of newly conceived chemical agents.

Biochemistry and pharmacology have had many valuable associations in the past and it may logically be anticipated that these sister sciences will continue to go forward in mutually profitable and happy collaboration.

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TEACHING ENDOCRINOLOGY BY THE EXPERIMENTAL METHOD

M. X. Zarrow
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Introduction

Endocrinology involves a study of the action of hormones; substances which are secreted by the glands of internal secretion and regulate the metabolic, functional, and morphogenetic activities of the organism. Classically endocrinology developed along with the study of anatomy and even today is taught in some of these departments. With increased knowledge, came an awareness of the role of the hormones in the economy of the body and the paramount influence they exert on physiological events. As a result it was soon classified as a subdivision of physiology.

However, it is apparent today that it would be most arbitrary to attempt to classify endocrinology under any of the major divisions of biology. Endocrinology has borrowed its techniques from physiology, pharmacology, biochemistry, organic chemistry, experimental embryology and many other allied fields and is briefly considered in the teaching of some of these courses. Such treatment is inadequate. Our knowledge of the hormones has grown to such an extent that it must be considered a discipline of its own.

The failure to teach endocrinology as such can only lead to an improper understanding of the subject. Rapid strides have been made in the last two decades and if the endocrinologist were to study only the physiology of the hormones, the work that is being done on the synthesis and the degradation of the steroids might be overlooked. Many other examples are available but the major point to remember is that classifications are arbitrary and can be dangerous if carried out too far. It is possible for the student to synthesize his basic knowledge of anatomy, histology, physiology, biochemistry and other fields in the study of endocrinology and not to take advantage of this would be poor pedagogy.

That endocrinology has been taught poorly in the past can be seen from a statement from Goodman and Gilman in their book "The Pharmacologic Basis of Therapeutics" published in 1940. They state..... "endocrine preparations are probably more often misused in therapy than any other group of drugs." How much more dangerous could that be today?

The recent discoveries of Kendall, Hensch and collaborators at the Mayo Clinic with regard to the therapeutic value of compound E or cortisone and the work of the chemists that have made both cortisone and adrenocorticotropin available for the physicians' armentarium have increased the danger of misuse. Within recent years much publicity has been given to all scientific discoveries and developments. This desire to keep the public informed of new developments is both commendable and dangerous. The danger lies in the fact that newspaper reports of scientific results are frequently garbled and never complete or adequate. This adds a further burden to the responsibilities of the professional man. For now it is his further duty to guide the public and keep people informed as to the true merit of new therapeutic agents.

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The Laboratory Course

Houssay, Nobel Laureate in medicine states in his textbook, Human Physiology, ..."Science in general and physiology in particular, can be taught properly only by intense practical and individual teaching, ... A book cannot be substituted for this kind of teaching; it can be no more than a useful guide." I would add to this that neither can the lecture substitute for the laboratory.

Proper use of the laboratory in the teaching of any scientific subject can be of inestimable value to the student. This is indeed true of endocrinology. A discipline that has borrowed its techniques from so many areas offers a wide variety of experiments for the student. It is only by working in the laboratory with the hormones and with the animals and by doing the experiments that the student will learn what these substances can do, how little is needed, what the side effects may be and the possible dangers involved in upsetting the fine balance present in the endocrine system.

For example treatment with a drug or hormone to correct a certain dyscrasia might easily affect other parts of the endocrine system. Estrogenic treatment can in time block the secretion of FSH from the pituitary and lead to ovarian atrophy. Likewise treatment with thiouracil for hyperactivity of the thyroid may if continued long enough lead to atrophy of the adrenal gland. This latter action involves the pituitary gland and its failure to secrete normal amounts of ACTH under such a regime.

The organization of a laboratory course in endocrinology involves primarily the need of an animal house and a laboratory for carrying out physiological and biochemical experiments. The size of the class will of necessity be limited by the space available for housing animals.

In a one semester course we have found it necessary to supply the following number of animals for 12 students; 300 mice, 200 rats, 60 hamsters, 4 rabbits and 12 frogs. It is possible to use only rats if one so desired,or mice as the case may be, however there are certain advantages to using the different species. To attempt to illustrate the different pregnancy tests would require rats, mice, rabbits and frogs. Cockerels are preferable for the bioassay of androgens and mice are more sensitive than rats in demonstrating the action of estrogens on the vaginal mucosa or the effect of gonadotropins on the uterus of the immature animal.

We have organized our laboratory course in endocrinology in two parts. One half the time is spent in routine class experiments that are performed by all students. The other half is spent on special problems which are assigned to a pair of students. There are frequent meetings in which round table discussions are held on the class experiments and the data obtained by the entire class is analyzed. Finally there is a special meeting held for the students to present their results on the individual problems and to answer questions from the other students. Thus the student not only benefits from his own work but also from the work of his classmates. The students work in pairs and are expected to spend 9 hours on their laboratory work. One 3 hour session per week is devoted to the class experiments and one 3 hour period to their special problem. The other 3 hours is accounted for in the time necessary for them to make daily injections or carry out daily observations.

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There are innumerable experiments available for laboratory exercises in endocrinology. It is possible to select certain experiments to demonstrate the activity of the principal hormones and certain outstanding techniques used in endocrinology. The experiments fall in one or both of the following categories; (1) surgical or operative techniques (2) action of hormones.

It is essential that the students learn the techniques involved in surgically removing the various endocrine glands and observe the deficiency symptoms and the effect of replacement therapy. The rat or the mouse are excellent animals for experiments on the removal of the gonads, adrenal glands, thyroid or pituitary. The first three operative procedures can be carried out with ease and require in addition to the animals only a minimum of surgical instruments and equipment. Hypophysectomies can be done only with a dissecting microscope possessing a long focal length and special light which can be focused with the microscope. However, here again by using the large bull frog, Rana catesbiana, it is possible to carry out the operation without special equipment.

It is routine for us to do several experiments involving the assay of hormones. These are excellent in that they not only demonstrate a bioassay procedure but also indicate certain of the physiological actions of the hormones.

In a semester course we spend approximately 4 to 5 weeks on the sex steroids, 4 weeks on the adrenal and thyroid and the remaining time on the pituitary gland, pancreas, pregnancy tests, regulation of water balance, hormonal factors in blood pressure, etc. The plan is to cover some function of all the hormones, to familiarize the student with all the endocrine glands and the action and interrelationship of their secretory products.

Possible Experiments for Use in the Laboratory and Procedures Available as Diagnostic Aids in the Clinic

Within recent years a multiplicity of techniques have become available as aids in the diagnosis of endocrinolopathies. Most of these procedures lend them nicely to laboratory experiments for class use. Many are now used routinely in the larger clinics and hospitals; some are still in the developmental stage. These procedures are concerned primarily with (1) the assay of hormones i.e. the determination of the concentration of the hormone in the urine, blood or other tissues by chemical or biological means and (2) the anatomical, histological and biochemical effects produced by the action or lack of action of the hormones.

Essentially the assay is still the most common technique used. Chemical determinations have been carried out for urinary ketosteroids, estroids and corticoids. These suffer from the need of elaborate extraction and purification and the lack of specificity in the reaction. Thus either the Kober reaction or the Zimmerman reaction involve a group of steroids and not a single substance.

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category belong the well known pregnancy tests and others for the various steroids and protein hormones. Testing as they do only an activity, elaborate purification is not required, hence there is little loss from such procedures. However, in instances where more than one substance have the same qualitative type of activity the assay fails to distinguish the type of substances but only summates the activity. Alberthas listed the following requirements for a good bioassay. These are (1) specificity (2) objectivity (3) precision (4) convenience (5) sensitivity. It is quite obvious that we cannot secure all of these requirements for an assay. Usually one or more of the requirements are sacrificed for sensitivity. This is still the most important objective for any bioassay. For example the determination of progesterone levels in the blood by the Hooker-Forbes test has only one of the above requirements, i.e. sensitivity. By this method it has been shown that a maximum concentration of approximately 12 µg. per ml. may be obtained. Using ultra violet spectroscopy and large amounts of blood, Haskins obtained 15 µg. per ml., a fairly good agreement.

The histological and anatomical changes are very important but it is not necessary to spend too much time on them here. Changes in the follicle cell height may be used as indication of thyroid activity, and similarly changes in the vaginal mucosa indicate estrogenic activity. Both of these phenomena have been incorporated into bioassays for the respective hormones.

Many biochemical tests are now in common usage in the clinic and are available for laboratory experiments involving endocrine activity. A few may be listed such as the determinations for blood sugar, calcium, chlorides, as well as the classical glucose tolerance and oxalate tolerance tests.

Pituitary Hormones

Adrenocorticotropin (ACTH)

ACTH stimulates the adrenal cortex and promotes the secretion of the corticoid hormones that are concerned with gluconeogenesis, protein catabolism, salt and water regulation. It is accepted now that the end effects of ACTH are similar to those of the adrenal cortex in that the result of ACTH injection is by virtue of corticoid release from the adrenal cortex.

Within the past few years the importance of ACTH and hence the adrenal cortex in the physiology of the organism and in certain dyscrasias such as rheumatoid arthritis has become well known. A number of investigators have shown that ACTH and cortisone have a therapeutic action in arthritis and other diseases of the mesenchyme. However, even prior to this Selye had formulated a hypothesis of hormonal action which led to his concept of the general adaptation syndrome. This is one of the first attempts to explain the interrelationship of the hormones and hormonal changes in the adaptation of the organism to its environment. Indeed, it is to be regarded as a milestone in the development of endocrinology. In this hypothesis the pituitary-adrenal cortical axis plays a major role and is used to explain the many changes both pathological and non-pathological that result from continued exposure to stress.

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upon (1) stimulation of the adrenal cortex resulting in increase of size of the gland, and (2) depletion of the ascorbic acid of the adrenal cortex. This latter has become the most commonly used procedure in view of its sensitivity and reliability. The test employs young, hypophysectomized rats and appears to be quite specific. One adrenal is removed prior to injection of the test material and the second adrenal is removed 1 hour after treatment. Except for the need of using hypophysectomized rats the test is not time consuming and can be completed in one day. The results are expressed as the difference between the concentrations of ascorbic acid in the adrenal gland of the animal before and after treatment and a dose response curve can be established. As yet, however, the technique is not sensitive enough for general use involving blood and urine. It may be necessary to obtain a more precise procedure or a method of concentrating the body fluids. However, it can be easily carried out by a class as a routine laboratory exercise.

Within the last several years the eosinopenia test has been used with much success. The procedure is highly sensitive and it depends simply upon determining the loss of circulating eosinophils from the blood. It has the advantage of requiring but a few minutes to complete and can be easily performed by any technician trained in doing blood counts. The eosinopenia develops within 4 to 6 hours and is the result of the action of the 11-oxycorticoids. As such it can be used to determine whether functional damage lies within the adrenal gland or with the pituitary. This latter technique is beginning to assume permanent importance in diagnosis of diseases involving the pituitary-adrenal complex.

Growth Hormone

The growth hormone has been used to a certain extent but as yet is not available in large amounts. The assays are inadequate for clinical use. They depend upon the gain in weight produced in the rat, (2) the resumption of growth in hypophysectomized animals or (3) changes in the skeletal system such as increased in width of the non-calcified cartilage. This latter test is three times as sensitive as the body weight test and requires only one-fourth the time.

Thyrotropin (TSH)

The assays for TSH in blood and urine involve changes in the weight of the thyroid gland of the chick. Modifications employing cell height changes have been developed and found to be more sensitive. However, none of these have been sensitive enough for routine use in the clinic. It is possible now that with the availability of I^{131}, more sensitive methods will be developed involving the uptake of this isotope. D'Angelo has recently used a test involving changes in the histology of the thyroid in young tadpoles. He has been able to detect TSH in the blood of different animals by this method. It is laborious and time consuming but opens the possibility for clinical use since it is highly sensitive.

Prolactin

Prolactin which is also known as luteotropin or LTH stimulates the crop sac of birds, lactation in mammals and appears to be responsible for the maintenance of the corpus luteum. At the present time, the only test of value with regard to sensitivity is that involving the crop sac. The material is injected into the crop sac and histological sections prepared.

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Some efforts have been made recently by Segaloff and his group to modify this procedure for the determination of prolactin in the urine of women. The sensitivity still appears to be inadequate for clinical uses although he was able to show differences depending on the reproductive state of the women.

Prolactin has also been used in rats and other experimental animals to induce pseudopregnancy and maintain deciduomata. Both of which are excellent laboratory exercises.

Follicle Stimulating (FSH) and Luteinizing Hormones (LH)

Clinical tests for gonadotropins have been carried out for many years. The Asheim-Zondek and many other pregnancy tests are based primarily on increased amounts of chorionic gonadotropin found in the urine. These gonadotropins are of placental origin and not from the pituitary gland. For the present we shall restrict ourselves to the pituitary gonadotropins. These are FSH which acts on the follicle of the ovary and stimulates spermatogenesis in the testis, LH which brings about ovulation in the female and stimulates the interstitial cells of the testis and prolactin or LTH which was mentioned above.

It is important to note that work has been done on the gonadotropin content of the urine but much care must be used in interpreting these results. The follicle stimulating hormone and the luteinizing hormone synergise in their action. Consequently the present bioassay technique for FSH is the result of the synergistic action of both FSH and LH and fails to differentiate the ratio of one to the other. However, valuable data for diagnostic purposes can be obtained and by comparison with normal values aid in the ultimate diagnosis.

In general the action of the pituitary gonadotropins are usually assayed in immature or hypophysectomized rats and mice as follows: by increase in ovarian weight, increase in uterine weight, premature opening of vagina, formation of corpora lutea, increase in weight of seminal vesicles, increase in weight of prostate, hyperemia of the ovaries, etc. The change in uterine weight of the mouse has been found to be sensitive and is used most commonly. It has been of value in the determining whether hypogonadism in the male is the result of pituitary or gonadal failure and has similar uses in the female. In other words, a total increase in gonadotropin units indicates that the pituitary is secreting an excessive amount due to the failure of the gonad to secrete its hormone and thus regulate pituitary function in the manner of the feedback mechanism. If the gonadotropins are decreased along with the gonadal steroids then the damage is probably in the pituitary gland.

Pregnancy Tests

There is now available a galaxy of different basic tests for pregnancy. These may be listed as follows: the Ascheim-Zondek test employing the mouse, the Friedman test employing the rabbit, the Xenopus test employing the South African frog, the hyperemia test using the immature rat and the test involving the release of sperm in the frog and toad. All of these appear to be highly sensitive and accurate and all involve the detection of chorionic gonadotropins.

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Neurohypophyseal Principle

The neurohypophysis secretes one or more active principles called the vasopressor, oxytocic and antidiuretic factors and influence blood pressure, uterine contractions and water balance respectively. Among the many tests that can be carried out for these substances are the classical ones involving the increase in blood pressure, increase in uterine contraction and a water retention. In the latter instance Burn and others have developed very sensitive techniques which involve the administration of water by lavage and the retention of this water as a result of antidiuretic hormone. This test has been used clinically with a certain amount of success.

Thyroid Hormone

Clinical tests of thyroid function consists of (1) basal metabolic rate, (2) protein bound iodine, (3) radioactive iodine, (4) blood cholesterol and (5) assay of calorigenic substances. The latter is based on the classical work of Gudernatsch and involves the appearance of limb buds in tadpoles, i.e. the metamorphosis of the frog.

The Adrenal Hormones

Tests for adrenocortical activity are numerous and involve many of those that have been mentioned for ACTH including tests peculiar to the adrenal itself. Determinations for 17-ketosteroids in the urine are routinely carried out for adrenal activity. In the female the source of this material is from the adrenal gland whereas in the male it arises from both the testes and the adrenal and consequently can also be used for gonadal function. A number of variations of the original Zimmerman reaction have been employed and have given about equal results. The determinations are made by fractional separation of the urine and development of a color with metadinitrobenzene. Marked changes in the excretion of the 17 ketosteroids may be noted in patients with dyscrasias involving the adrenal cortex or testis. In Addison's and Simmond's disease the ketosteroids are reduced and may even be totally lacking in the female. Masculinizing syndromes involving the adrenal gland may cause a rise in the 24 hour output of the ketosteroids from a normal of 12-20 to as much as several hundred milligrams.

The 17-ketosteroids probably depends upon an androgenic producing effect of the adrenal cortex. However, one of the most important class of steroids produced by the adrenal glands is a group of substances referred to as the 11-oxycorticoids. These are the substances that are concerned with carbohydrate and protein metabolism. This group of substances which includes cortisone has an action on the glycogen content of the liver. Venning has devised as assay involving the glycogenic action of the corticoids on the liver in adrenalectomized mice. This assay has been found to be sensitive and although laborious has been used with quite some success in the clinic in determining hormone concentrations in the urine.

Several chemical methods have been developed for the determination of 11-oxycorticoids. None of them are particularly specific and vary greatly from the bioassay procedures. These chemical methods are based on the liberation of formaldehyde from urinary extracts by periodic acid or by measuring the reducing action of steroids using a suitable copper reagent or phosphomolybdic acid. The first method probably measures both glyco-

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genic and non-glycogenic steroids.

It should also be pointed out that the eosinopenia test is extremely sensitive and can be used for the determination of 11-oxycorticoids. Adrenalectomized animals are extremely sensitive to small amounts of this hormone. Finally the maintenance of life in adrenalectomized rats has been used but requires large amounts of hormone.

Gonadal function in the male is based upon tests which determine the 17 ketosteroids or urinary androgens possessing biological activity. The comb growth test in cockerels is still the most sensitive bioassay for androgens. Direct application of an ethyl alcohol extraction of urine to the comb of a young cockerel will detect as little as 20 µg. equivalent of testosterone. However, the test still seems to be inadequate for blood determination.

Ovarian activity is determined by tests for the estrogenic or the progestational hormones. The classical tests for estrogens involving vaginal smears of castrated mice or rats is still one of the best assays. As could be expected many assays for estrogen have been published. All of them are concerned with one of the physiological actions of hormone, such as increase in uterine weight or water as well as many others. A colorimetric test has been described by Kober and many modifications have been subsequently published but as yet it is difficult to evaluate the chemical tests in that they lack specificity and do not correlate well with the bioassays.

Until 1946 the major assay for progesterone activity was based upon progestational reaction of the uterus of rabbits. It has never been found as such in the urine though many investigators have noted the presence of pregnanediol which is believed to be a degradation product of progesterone. A number of extremely satisfactory procedures have been developed for chemically determining pregnanediol in the urine and these have been used routinely in some clinics. Recently, however, Hooker-Forbes have discovered that progesterone produces certain changes in the cells of uterine stroma of a castrated mouse. These changes were found by the investigators to be highly specific for progesterone and although the test is laborious its sensitivity is such as to make it applicable for blood. This procedure detects amounts of progesterone as small as 0.0002 µg. The procedure is being used now to determine levels in the blood during normal menstrual cycles and during pregnancy. It has been shown recently that the hormone is present in the proliferative phase of the menstrual cycle indicating that progesterone may be secreted from some source other than the corpus luteum.

A number of tests and bioassays have been briefly described though no attempt was made to be all inclusive. It should be indicated in conclusion that all these procedures can be used for laboratory exercises and add much to the practical and theoretical value of such a course.

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THE ACTIVITIES OF THE DIVISION OF PHARMACOLOGY OF THE UNITED STATES FOOD AND DRUG ADMINISTRATION

Bert J. Vos, M. D.
Division of Pharmacology, Food and Drug Administration,
Federal Security Agency, Washington, D. C.

The Food and Drug Administration is a part of the Federal Security Agency. Its main function is the enforcement of the Federal Food, Drug, and Cosmetic Act, which prohibits interstate commerce in adulterated or misbranded foods, drugs and cosmetics. In addition, it enforces the Caustic Poison Act, the Tea Importation Act, the Filled Milk Act, and the Import Milk Act. The Harrison Narcotic Act, on the other hand, is enforced by the Treasury Department, while sera, vaccines and arsphenamines are manufactured under license from the National Institutes of Health.

The Division of Pharmacology is one of the eight scientific divisions of the Food and Drug Administration. The others are the Divisions of Antibiotics, Cosmetics, Food, Medicine, Microbiology, Nutrition, and Pharmaceutical Chemistry.

Our division has a staff of 55. Of these, 25 have scientific training; the remainder consist of animal caretakers, laboratory assistants and the secretarial force.

In this talk I will cover chiefly the work of the Division of Pharmacology in the control of drugs, but there are two points which should be made clear at the outset: First, that a large share of the drugs are examined not in the Division of Pharmacology but rather in the chemical laboratories of our 16 districts which are distributed throughout the country. Only those drugs which have to be tested on animals come to us in Washington. Secondly, that the control of drugs is only a part of the work of the Division of Pharmacology. We also test foods and cosmetics. As a matter of fact, the study of the toxicology of food additives, which include such things as preservatives, antioxidants, emulsifiers, synthetic sweetening agents, agricultural insecticide residues, etc., is one of our more time-consuming activities. We are particularly concerned with the possibility of the long-term effects from very small amounts in the diet and consequently our tests frequently run as long as 2 years in rats and even 4 or 5 years in dogs.

The bulk of our drug control work is done under what we call the project schedule. At the close of each year the results of the preceding 12 months are reviewed and after taking any new developments into consideration a program for each bioassay drug is mapped out for the coming year. Each of the 16 geographic districts is assigned a quota of samples for collection which is proportioned to the number of manufacturers of that particular drug located in the district. The collection of these samples is timed to provide steady flow of samples to our laboratory. Sufficient leeway is provided in this schedule to permit the examination of additional samples which arise as a result of "consumer complaints", and to follow up new violations which are uncovered as the year progresses. Since drugs ordinarily come under the jurisdiction of the Food and Drug Administration only if they have been in interstate commerce or are offered for shipment in interstate commerce, it is necessary for our

THE ACTIVITIES OF THE DIVISION OF PHARMACOLOGY OF THE UNITED STATES FOOD AND DRUG ADMINISTRATION

Bert J. Vos, M. D.
Division of Pharmacology, Food and Drug Administration,
Federal Security Agency, Washington, D. C.

The Food and Drug Administration is a part of the Federal Security Agency. Its main function is the enforcement of the Federal Food, Drug, and Cosmetic Act, which prohibits interstate commerce in adulterated or misbranded foods, drugs and cosmetics. In addition, it enforces the Caustic Poison Act, the Tea Importation Act, the Filled Milk Act, and the Import Milk Act. The Harrison Narcotic Act, on the other hand, is enforced by the Treasury Department, while sera, vaccines and arsphenamines are manufactured under license from the National Institutes of Health.

The Division of Pharmacology is one of the eight scientific divisions of the Food and Drug Administration. The others are the Divisions of Antibiotics, Cosmetics, Food, Medicine, Microbiology, Nutrition, and Pharmaceutical Chemistry.

Our division has a staff of 55. Of these, 25 have scientific training; the remainder consist of animal caretakers, laboratory assistants and the secretarial force.

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inspectors to locate samples which have crossed state lines and to get documentary proof that such a crossing occurred. When such a sample is located the inspector purchases it, or as much of it as is needed for assay purposes, from the consignee, and sends it under seal to our laboratory.

The tests conducted on a project basis in our division include bioassays to determine the potency of such drugs as epinephrine, posterior pituitary, digitalis, and chorionic gonadotropin, and the examination of parenteral solutions for the presence of pyrogens. In these tests we follow the methods described in the U. S. Pharmacopoeia and the National Formulary, or in the case of an unofficial drug such as chorionic gonadotropin we follow the most generally recognized methods. If a sample upon assay does not meet the standards of the official compendium, or in the case of an unofficial product, fails to meet the potency declaration set forth on its own label, the analyst first of all repeats his assay. If he checks his own result the sample is turned over to a check-analyst who performs his assay without knowledge of the first analyst's results. In some instances this checking process is carried even further and we submit the sample to an analyst outside of the Food and Drug Administration. Only after we are completely satisfied with the accuracy of the results is legal action undertaken.

Insulin differs from the other drugs handled in our division in that every batch is tested by us before it is distributed by the manufacturer. In some cases our tests include a complete bioassay. In other cases we review the bioassay data submitted to us but check the chemical analyses in our own laboratory. The Division of Antibiotics maintains a similar certification service for certain of the antibiotic drugs.

A second type of drug sample which comes to us for analysis is the so-called consumer complaint sample. These form a very valuable addition to the spot-checking which is done under our project schedule, and I would like to impress on each of you the importance of referring to the Food and Drug Administration any drug product which is suspected of adulteration. As might be expected, the consumer complaints cover a wide range. The following may be cited as typical: An estrogenic preparation which the purchaser suspected of being subpotent because it had been offered considerably below market price. A batch of 10% calcium gluconate solution which produced fever when injected. A local anesthetic solution which gave stinging followed by sloughing at the injection site. A children's laxative which produced vomiting. A worm medicine for hogs the use of which was associated with fatalities. In each case our first problem is to determine whether the drug is at fault. Sometimes this can be decided by trying it on animals. More often the reaction complained of bears enough resemblance to the known side effects of the drug that the problem can be resolved only by taking the suspected material and comparing it in animals with an authentic sample of the same drug. Once it has been established that the suspected drug is at fault the problem broadens out. An attempt is made to identify the offending contaminant. Additional samples of the firm's product are collected to determine what lot numbers are involved. Our inspectors visit the factory and try to find out how the mistake occurred. If a serious health problem is involved, the firm is urged to recall the offending material from the market. If necessary, outstanding stocks of the drug are seized. At a later date the manufacturer is given an opportunity at a hearing to explain why he thinks he or his

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firm should not be prosecuted.

The research activities of our division are extensive and varied. Their object is to develop information which will help us in enforcing the Food, Drug, and Cosmetic Act. In the drug field our research is directed toward developing new bioassay techniques, or improving old ones, and where possible working out chemical methods to replace the biological ones. From this last you might imagine that our bioassayists were trying to work themselves out of a job. So far the appearance of new drugs requiring bioassay has kept pace with those for which bioassay is no longer needed. We also study the rate of deterioration of drugs under various storage conditions. The importance of this type of information to us is that when our assays show low potency in a sample we have to be able to establish that it was subpotent at the time it was shipped by the manufacturer.

Another phase of our research activity consists in studying the pharmacodynamics and toxic side reactions of new drugs. It is, of course, the responsibility of the manufacturer to supply such information when he files a New Drug Application, but occasionally there are circumstances which make it necessary for us to develop such data ourselves.

There are several less direct but nonetheless important ways in which we control drugs. One of these is in reviewing the pharmacological data in the New Drug Applications which are submitted to the Division of Medicine before a new drug is put on the market. Another is the advice which we give either by correspondence or at interviews regarding the safety of proposed drug products and the type of tests which we regard as essential for establishing their safety.

In closing, I should like to mention two publications which will assist you in following the activities of the Food and Drug Administration. One of these is the Annual Report of the Food and Drug Administration which is reprinted from the Annual Report of the Federal Security Agency and obtainable from the U. S. Government Printing Office at nominal cost. The other is the Notices of Judgment which contain a record of our court actions which have terminated. These are obtainable upon request from the Food and Drug Administration. The results of our research work are, of course, published in the regular scientific journals when of sufficient general interest.

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K. K. Chen
Eli Lilly and Company, Indianapolis, Indiana

I. Research in Pharmaceutical Industry
   1. Reasons
   2. Principles
   3. Step-by-step development
   4. Screening program

II. Choice of Methods
   1. Specificity
   2. Speed
   3. Economy
   4. Indirect approaches

III. Toxicity
   1. Lethal dose by a single application
   2. Prolonged administration
   3. Pathological studies

IV. Pharmacodynamics
   1. Precise mechanism of action
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   3. Elimination
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V. Clinical Investigation
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VI. Uses of Results
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- B. The Pituitary-adrenocortical System

II. Methods for ACTH Assay

- A. Adrenal Ascorbic Acid Depletion
  - 1. Sayers' Method
  - 2. Munson Modification
- B. Other Measures of Adrenal Response
  - 1. Maintenance
  - 2. Repair

III. Tests for Cortisone-like Activity

- A. Work Test - Ingle
- B. Growth Test - Grollman
- C. Effect on Hematopoietic System
  - 1. Eosinophils - Speirs
  - 2. Lymphocytes - Dougherty
- D. Gluco-corticoid Activity by Liver Glycogen Deposition
  - 1. Rats - Reinecke
  - 2. Mice - Venning
- E. Experimental Production of Arthritis
  - 1. Polyarthritis - L Pleuropneumonia - Kuzell
  - 2. Joint Arthritis - Selye
- F. Effect on Cell Permeability
  - 1. Clearance of Dye from Joint - Seifter
  - 2. India Ink Diffusion - Opsahl
- G. Effect on Tissue Repair
  - 1. Wound Healing - Ragan
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Adrenergic-Blocking Agents

F. G. Henderson and K. K. Chen
Eli Lilly and Company

I. Introduction
   A. Definition of an "adrenergic-blocking agent" (1)
   B. Types of compounds which produce adrenergic-blockade
      1. Ergot alkaloids (2)
         a. Ergotamine
         b. Ergotoxine
      2. Benzodioxanes (4)
      3. Imidazolines (3)
      4. Yohimbine
      5. β-Haloalkylamines (5)

II. Screening Procedures
   A. Alteration of the pressor response to epinephrine in the anesthetized cat
   B. Intravenous toxicity in albino mice
   C. Oral toxicity in rats
   D. Subacute toxicity in rats

III. Other Pharmacologic Studies
   A. Effectiveness of blockade against massive doses of epinephrine
   B. Action against other pharmacologic effects of epinephrine
      1. Relaxation of the non-pregnant cat uterus
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C. Blockade of sympathetic nerve stimulation
   1. Pressor response to splanchnic nerve stimulation
   2. Retraction of cat nictitating membrane following stimulation of postganglionic sympathetic fibers

IV. Preliminary Clinical Testing
   A. Dose selection
   B. Observation for side-effects, such as nausea, vomiting, etc.
   C. Alteration of pressor response to epinephrine

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Antihistaminic and Antispasmodic Screening

Henry M. Lee and K. K. Chen
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Antihistaminic tests

1. Isolated guinea pig ileal segment
   a. Apparatus
   b. Procedure
   c. Example

2. Guinea pig aerosol
   a. Apparatus
   b. Procedure
   c. Example

3. Additional tests
   a. Blood pressure respiration anesthetized animal
   b. Anaphylactic shock protection
   c. Whealing reaction

6. Blockade of sympathetic nerve stimulation
   1. Pressor response to splanchnic nerve stimulation
   2. Retraction of nictitating membrane following stimulation of postganglionic sympathetic fibers

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3. Additional tests
   a. Blood pressure respiration anesthetized animal
   b. Anaphylactic shock protection
   c. Wheal-flare reaction

Antispasmodic tests

1. Isolated guinea pig ileal segment
2. Thiry fistula dog
   a. Example
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   a. Salivary secretions
   b. Vagal inhibitory
   c. Hunger contraction

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Screening Analgesics

E. Brown Robbins and K. K. Chen
Eli Lilly and Company

I. Magnitude of the Analgesic Screening Program
   A. Interest in potent synthetic compounds
   B. Interest in non-narcotic mild analgesics of codeine potency

II. Requirements of Testing Methods
   A. Practical for large number of tests
   B. Sensitive
      1. Between different drugs
      2. Between different doses of same drug
      3. Reveal so-called mild type of analgesia
   C. Meaningful
      1. Metabolism in experimental animal similar to man's
      2. Results parallel subsequent clinical findings

III. Methods Available
   A. Mechanical - vonFrey hairs (1) - Haffner tail pinch (2)
   B. Chemical - little used - 0.2 cc. of 1% silver nitrate into ankle joint (3)
   C. Electrical - tooth pulp (4, 5)
   D. Thermal - most widely used
      1. Hardy-Wolff-Goodell (6)
      2. D'Amour-Smith (7)
      3. Woolfe-Macdonald (8)
   E. Pharmacological or Physiological
      1. Ischemic muscle (9, 10)
      2. Visceral pain (11)

IV. Our Choice of Screening Methods
   A. Rat tail heat - similar to that of Davies (12)
      1. Satisfies requirements of speed and sensitivity
   B. Hardy-Wolff-Goodell (13)
      1. Human - training - conservative dosage - blind medication
      2. Dog - reliability of end point (14) - metabolism may be misleading

V. Addiction Studies
   A. USPHS Hospital - Lexington, Ky.
   B. Drs. Vogel, Isbell, Wikler and Eddy

VI. Conclusion
   A. Criticism of cutaneous pain methods
   B. Final answer always from clinical results

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STATISTICAL ANALYSIS OF BIOLOGICAL DATA

A. C. Bratton, Jr.
Pharmacology Dept., Parke, Davis & Co.
Detroit, Michigan

I scarcely need to mention the fact that no two animals in a cage of several hundred are alike in every respect. The pharmacologist continually strives to determine the quantitative effects of substances on entire animals, bits of tissue, or even single cells. How many individual units should he study in order to make a reasonable estimate of the mean response of the population of units from which his sample was drawn? Statistical methods provide an intelligent answer in many cases, and many scientific journals require authors submitting papers to analyze their data by such procedures. The problem is not confined to the biological sciences. We are often inclined to think of an analytical balance or a cathetometer as instruments of high reliability, and yet repetitive weighing of a fixed mass or measurement of a fixed length results in a scatter of observations around a mean value. It appears that our friends in chemistry or physics are also bothered by the problem of variability!

The animals to be used in a quantitative experiment or assay may have already been selected at the outset by certain criteria, such as species, strain, sex, age, or weight. The final division of the animals into test groups to receive various treatments must be done by a method designed to randomize the individuals among the test groups. The assignment of a numbered card to each animal and the drawing of these cards from a shuffled deck is a convenient method of accomplishing this. It goes without saying that throughout the conduct of the ideal experiment, all but one independent variable must be held constant. The order of administration of treatments may also be profitably randomized, in order to avoid the biasing effect of drifts of manual or technical skills during the administration. An excellent discussion of some of the unique problems of designing statistically sound human experiments, many of which are common to animal experiments in general, may be found in the very readable "Principles of Medical Statistics", by Bradford Hill.

Confession is good for the soul, and I would like to confess at the outset that I am not a statistician, but only a rather naive user of some of the simpler applications of biometry to pharmacological data. Time permits only brief mention of some of the more useful elementary methods, with a few references to sources where more detailed information on these and more refined procedures may be found. The illustrations chosen involve samples of twenty or more observations; quite frequently in the laboratory there are fewer observations, and correction factors must be applied to the standard statistical formulae to deal adequately with these small numbers. The complexities of these small-number problems lie beyond the scope of this discussion.

We are all familiar with the type of experiment where some single measurement is made on each individual in a sample taken from a large group, or population. Figure I illustrates the values of systolic blood pressure taken on 20 individuals. No doubt these individuals may have had some properties in common: they may have represented a certain age group, or a given sex, or a common racial origin. For our purposes, these other

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possible properties are not under scrutiny. Our present problem is to gain some idea of a larger population with respect to systolic blood pressure from the data collected on this sample of 20 individuals. There is no need to dwell on the usefulness of the mean, or arithmetic average, of the observed values as a convenient descriptive unit. What can be done to describe in accurate terms the scatter of the observations around the mean? The Standard Deviation, usually represented by the Greek letter sigma, is a statistical means of accomplishing this. The deviation from the mean of each observation is squared, and the sum of squares of these deviations is totaled. In the formula, N refers to the number of items in the sample, and the term, N-1, is referred to as the "degrees of freedom". Knowing the total, N-1 items making up the sum must be calculated separately, but the final single item may be obtained by difference. For our series, the standard deviation is 13.9. It will be seen that the standard deviation places greater emphasis on extremes from the mean than on values which lie close to the mean.

FIGURE II

Let us arrange our 20 observations on blood pressure in the form of what is called a frequency distribution, as shown in Fig. 2. We first group the observations into classes, in this case pressures of 5 millimeters. When the number of observations falling in each 5 millimeter range is plotted as shown, the frequencies rise to a maximum around the mean, and then decline. This type of plot is called an histogram. Had our sample contained a very large number of individuals, the histogram would become much more regular in contour, and would eventually present a bell-shaped outline. When the curve is symmetrical about the mean, it is spoken of as a normal frequency distribution curve. At least six other types of distribution curves have been described, which differ from the normal curve in that they are <u>not</u> symmetrical about the mean. The methods of handling data have been much better worked out for the normal distribution than for other varieties, so it is always the hope of the worker using statistical methods that his data fit a normal curve, or can be transformed to a normal curve by some simple means. If we lay off one standard deviation from either side of the mean, as is shown, the area of this portion of the distribution corresponds to 68.3% of the total area; the area enclosed by two standard deviations on either side of the mean is 95.5%, and that by three standard deviations on either side 99.7% of the area. Thus, if the items in our sample are normally distributed, roughly two-thirds of them should fall within one standard deviation of the mean, and roughly 95% within two standard deviations on either side of the mean. Practically all of the values fall within a distance of three standard deviations on either side of the mean. It is obvious that the standard deviation is a very useful measure of the scatter of observations in a set of data. The total range of observation is about six times the standard deviation. Methods are available for plotting the theoretical normal distribution curve of a set of data, as has been done in the figure, and by means of Karl Pearson's chi square test, the goodness of fit of the observed data to the theoretical curve may be determined.

Suppose another group of 20 individuals from another population is measured as before. Does this sample differ significantly from the first sample? To answer the question, the mean and standard deviation are calculated as before. The standard error of the difference of the mean is calculated as indicated in Fig. 3. If the difference in two means is

possible properties are not under scrutiny. Our present problem is to gain some idea of a larger population with respect to systolic blood pressure from the data collected on this sample of 20 individuals. There is no need to dwell on the usefulness of the mean, or arithmetic average, of the observed values as a convenient descriptive unit. What can be done to describe in accurate terms the scatter of the observations around the mean? The Standard Deviation, usually represented by the Greek letter sigma, is a statistical means of accomplishing this. The deviation from the mean of each observation is squared, and the sum of squares of these deviations is totaled. In the formula, N refers to the number of items in the sample, and the term, N-1, is referred to as the "degrees of freedom". Knowing the total, N-1 items making up the sum must be calculated separately, but the final single item may be obtained by difference. For our series, the standard deviation is 13.9. It will be seen that the standard deviation places greater emphasis on extremes from the mean than on values which lie close to the mean.

FIGURE II

Let us arrange our 20 observations on blood pressure in the form of what is called a frequency distribution, as shown in Fig. 2. The first group the observations into classes, in this case pressures of 5 millimeters. When the number of observations falling in each 5 millimeter range is plotted as shown, the frequencies rise to a maximum around the mean, and then decline. This type of plot is called an histogram. Had our sample contained a very large number of individuals, the histogram would become much more regular in contour, and would eventually present a bell-shaped outline. When the curve is symmetrical about the mean, it is spoken of as a normal frequency distribution curve. At least six other types of distribution curves have been described, which differ from the normal curve in that they are not symmetrical about the mean. The methods of handling data have been much better worked out for the normal distribution than for other varieties, so it is always the hope of the worker using statistical methods that his data fit a normal curve, or can be transformed to a normal curve by some simple means. If we lay off one standard deviation from either side of the mean, as is shown, the area of this portion of the distribution corresponds to 68.3% of the total area; the area enclosed by two standard deviations on either side of the mean is 95.5%, and that by three standard deviations on either side 99.7% of the area. Thus, if the items in our sample are normally distributed, roughly two-thirds of them should fall within one standard deviation of the mean, and roughly 95% within two standard deviations on either side of the mean. Practically all of the values fall within a distance of three standard deviations on either side of the mean. It is obvious that the standard deviation is a very useful measure of the scatter of observations in a set of data. The total range of observation is about six times the standard deviation. Methods are available for plotting the theoretical normal distribution curve of a set of data, as has been done in the figure, and by means of Karl Pearson's chi square test, the goodness of fit of the observed data to the theoretical curve may be determined.

Suppose another group of 20 individuals from another population is measured as before. Does this sample differ significantly from the first sample? To answer the question, the mean and standard deviation are calculated as before. The standard error of the difference of the mean is calculated as indicated in Fig. 3. If the difference in two means is

twice the standard error of the differences of the means, the observed means could have been seen in samples from the same population in about 5 out of 100 trials. In biological work, it is common practice to consider odds of 5 in 100, or a probability of .05, to be the borderline between unlikely and likely events. If the difference in means is three times the standard error of the difference, the odds are about 3 in 1000 that the means could have been observed in samples from the same population, which is a highly unlikely event. In this case, our difference is even greater than 3 times the standard error of difference of the means, so we conclude that our samples really were taken from different populations.

The 'student "t" test' is frequently used to determine if two samples or more properly, the populations from which they were drawn, differ significantly from one another. In Fig. 4 are two series of litter-mate rats fed four weeks, with the terminal weight gains listed. The difference of each pair of items in the two columns is determined, and the mean, standard deviation, and standard error of the mean are calculated. The term, "t", is defined by the mathematical formula; M is the true mean of the differences. Assume for a moment the hypothesis that there is no difference in the two populations represented by the two groups. M becomes 0, and "t" equals 2.70. Most statistical texts contain a table listing "t" values for various degrees of freedom and various levels of significance. The observed value of "t" indicates that the hypothesis would be true fewer than five times out of 100, and hence the hypothesis is false. Therefore, there <u>is</u> a significant difference between the two groups.

A very useful test of significance of attribute data is the chi square test. In Fig. 5 are tabulated the numbers of live births seen in each 3-hour period. Does this distribution differ significantly from one that might have occurred by chance? In a chance or random distribution, the expected values of the entries would tend to be equal. We set up the hypothesis that the observed and expected population do not differ significantly, and prove whether the assumption is true or false. The expected value is subtracted from the observed and squared, and the squares divided by the expected value. Chi square is the sum of these quotients. Tables are available in standard texts relating chi square, probability, and n, the degrees of freedom. In this example, the probability of our hypothesis being true is extremely remote, so the observed distribution could not have been expected to happen by chance. This allows the experimenter to seek some other explanation, presumably biological in character, for the observed distribution.

An extremely useful application of the chi square test is the fourfold table, which is one containing four entries. In the example shown, in Fig. 6, two groups of 50 mice have been inoculated with a microorganism, and one group of 50 has been subjected to some type of treatment, the problem being to decide whether the treatment favorably influenced the survival rate of the mice. For perfect correlation of treatment with survival, all items would be clustered into two of the opposite corners of the "box". In the case of no correlation, each of the four corners of the "box" would have an equal number of items. Again, we set up the hypothesis that the observed results could have occurred by chance and test its validity. The probability of validity of the hypothesis is 0.2 to 0.3, which means it would be true in 20 to 30% of the trials. We must

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conclude that the hypothesis is true in this case, and that our treatment has not significantly protected the mice.

The two main types of responses involved in bioassays are the graded response, in which each animal is separately measured for some property (such as blood glucose or blood calcium levels), and the all-or-none or quantal response, in which an animal is classed simply as a reactor or non-reactor. Let us first consider the quantal response.

When the percentages of death among animals in groups injected with successively large doses of a toxic drug are plotted, a curve somewhat like a parabola results. On plotting percentage response against log dose, a sigmoid curve usually results. Gaddum found that when percentage response was transformed to "normal equivalent deviation units", and the transforms plotted against log dose, a straight line resulted. Later, Bliss replaced normal equivalent deviation units by a more convenient unit, the probit, which is now widely used. Subsequently, other types of transforms have been suggested, but these lie beyond the scope of this discussion. Data are easier to analyze by statistical methods when they can be represented by the equation of a straight line. The dose-response curve is most stable around the point of 50% response (probit value 5), hence the widespread acceptance and use of such terms as LD_{50} and ED_{50}. In a bioassay, one compares the effects of an unknown and a standard treatment in groups of animals drawn from the same population. If the qualitative effects of the two treatments or substances are the same, the log-probit regression lines should be parallel, and a relative estimate of potency is made by comparing the ED_{50} dose of the unknown with the ED_{50} dose of the standard. An estimate of error, that is, the confidence limits of the potency ratio, should always be provided in a bioassay. A convenient graphical solution of this type of problem was proposed by Litchfield and Fertig; Bulletin of the Johns Hopkins Hospital, Vol. 69, page 276 (1941). Later, Litchfield and Wilcoxon; Journal of Pharmacology and Experimental Therapeutics, Vol. 96, page 99 (1949) adapted the original method to one using monograms to further simplify the computations involved, and also added a means of fitting the best regression line to the data by the method of least squares. Certain restrictions are imposed on the spacing of doses in order to simplify calculation.

The use of the original method of Litchfield and Fertig is illustrated in Fig. 7 with a bioassay of digitalis by the frog method. Fifteen frogs were used for each of the three doses of unknown and of standard. The three ascending doses of unknown killed 2 out of 15, 5 out of 15, and 10 out of 15, respectively, and the three ascending doses of standard killed 2 out of 15, 5 out of 15, and 8 out of 15, respectively. These responses are first converted to percentage response, which in turn are converted to probit units from a table. Dotted regression lines are first drawn for unknown and standard, fitting these lines by eye to the plotted points. If the unknown and standard differ qualitatively in pharmacological properties, the slopes of the regression lines are usually significantly different. In this case, where we are comparing a standard with an unknown of the same properties, it is justifiable to assume the slopes of the two curves are identical. However, a mathematical method is available to test this point if desired. In the present case, it can be shown that the slopes are not significantly different. Let us deliberately re-draw the two regression lines with the same slope, for there is a statistical advantage in so doing. The points where the regression lines

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cross the probit 5 mark are the log ED_{50} values. The slope of the regression line is determined by laying off a triangle with the regression line as hypotenuse, and determining the ratio of opposite over adjacent sides of this triangle. The standard deviation of a unit observation is the reciprocal of the slope. The standard error of the slope is calculated as shown. The log ED_{50} is analogous to the mean in the usual statistical formula. The standard error of the log ED_{50}'s and the standard error of the difference of the log ED_{50}'s are calculated. Since the means are logarithms, the difference of the means is the log of a ratio—in this case, the relative potency. Addition or subtraction of twice the standard error of the difference to this log potency gives two logarithms, the antilogs of which represent the range to be expected in 95 out of 100 replicate trials of the assay, or the 95% confidence limits.

The quantal type of bioassay is applicable to a variety of problems, such as a comparison of lethality of two drug samples, and the chemotherapeutic trial of agents against otherwise lethal experimental infections.

A bioassay based on a graded response is too complicated in design and mathematical treatment to be adequately discussed in a few minutes. As in the quantal problem, a transformation is sought which will rectify the relationship between dose and response to yield a straight line. From two to four dose levels are usually employed for the unknown, and usually an equal number for the standard, although some assays are designed with only a single dose of standard. The precision of such an assay is improved by use of a factorial design, which balances the controllable variables in the assay. Frequently provision is made for each animal or animal group to receive at least one or more dose levels both of standard and unknown. This cross-over arrangement increases the amount of information available from each animal, with the result that the bioassay may be many times as efficient with respect to numbers of animals used as a quantal type of assay. The statistical analysis usually involves an analysis of variance, in which the variance contributed by a number of factors (such as within animal groups, between groups, between types of treatment, etc.) can be separately examined. The professional statistician regards analysis of variance, and a rather related procedure, the analysis of covariance, as among the most useful tools at his disposal.

Statistical methods are rapidly coming into use in connection with quality control methods for manufactured articles of every sort. Sampling of finished products by approved methods allows of confidence in predicting the quality of the entire output of a plant. Statistical analysis is of course an accepted and expected part of a quantitative biological experiment. Not only do the methods provide a basis for evaluation of the data, but may suggest improved ways of conducting the experiment. It is important to realize that statistical analysis cannot be expected to salvage a poorly designed or poorly executed experiment, but it can be a welcome adjunct to the judgment of the experimenter.

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Fig. 1. DETERMINATION OF STANDARD DEVIATION OF A SERIES

Systolic b.p. (X)	Dev. from Mean (X-m)	Square of Dev.	Systolic b.p. (X)	Dev. from Mean (X-m)	Square of Dev.
98	- 30	900	123	- 5	25
160	32	1024	125	- 3	9
136	8	64	129	1	1
128	0	0	132	4	16
130	2	4	154	26	676
114	- 14	196	115	- 13	169
123	- 5	25	126	- 2	4
134	6	36	132	4	16
128	0	0	136	8	64
107	- 21	441	130	2	4
			Σ 2560	0	3674

Sum of blood pressure observations, 2560. Mean, 128.
Sum of deviations from mean, 0.
Sum of squares of deviations from mean, 3674.

$$\text{S.D. } (\sigma) = \sqrt{\frac{\Sigma (X-m)^2}{N-1}} = \sqrt{\frac{3674}{19}} = 13.9$$

Fig. 2. FREQUENCY DISTRIBUTION OF A SAMPLE

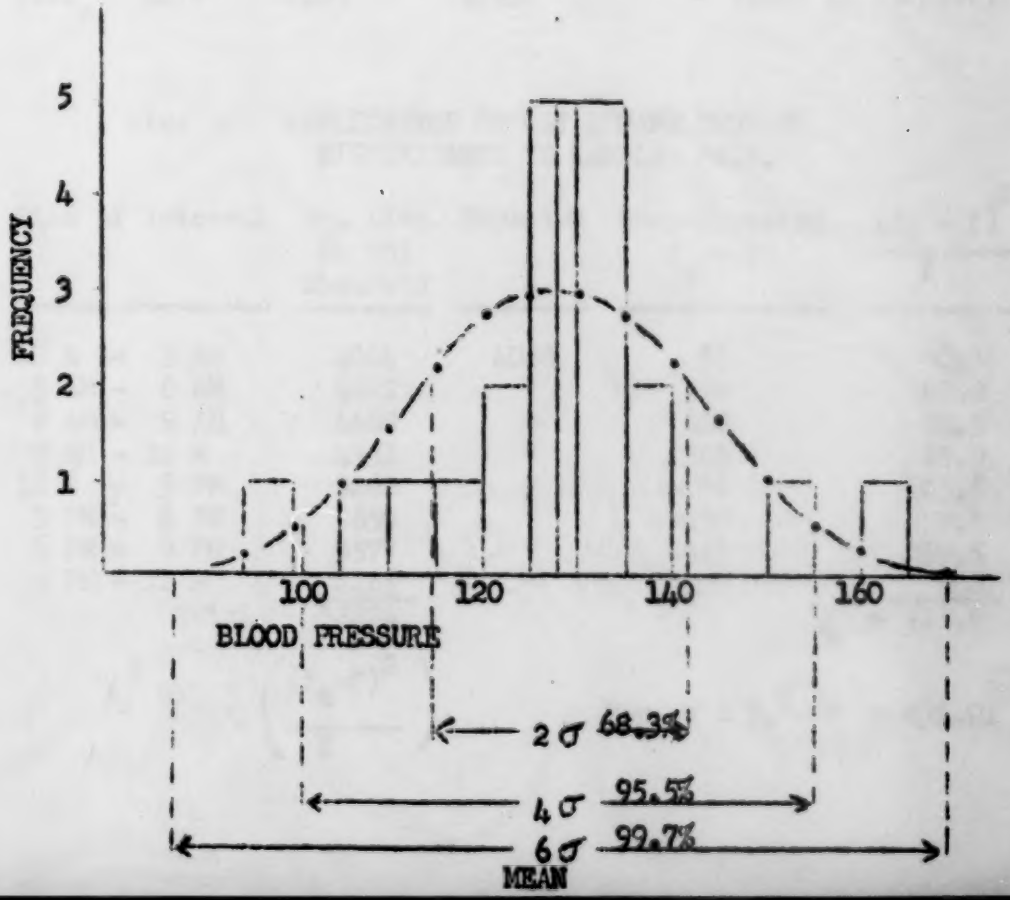

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Fig. 2. FREQUENCY DISTRIBUTION OF A SAMPLE

Fig. 3. ASSESSMENT OF SIGNIFICANCE OF DIFFERENCE OF TWO MEANS.

	Mean	S.D.	N (No. of Items in Sample)
Sample 1	128	13.9	20
Sample 2	100	10.5	20
Difference	28		

Standard error of difference of two means =

$$\sqrt{\frac{(S.D._1)^2}{N_1} + \frac{(S.D._2)^2}{N_2}} = \sqrt{\frac{(13.9)^2}{20} + \frac{(10.5)^2}{20}} = 3.9$$

Fig. 4. FOUR-WEEK WEIGHT GAINS IN LITTER-MATE WEANLING RATS.

			Difference
	81	85	4
	99	93	- 6
	58	77	19
	55	62	7
	77	98	21
	62	90	28
	64	59	- 5
	68	82	14
	57	95	38
Mean	69.00	82.30	13.33
S.D.	14.34	8.96	14.80
$S.E._m$	4.78	2.99	4.93

$$t = \frac{\text{mean of difference} - M}{S.E._m}$$

$$= \frac{13.33 - 0}{4.93} = 2.70$$

For 8 degrees of freedom,
t = 2.306 at 5% level
= 3.355 at 1% level

Fig. 5. APPLICATION OF CHI SQUARE TEST OF SIGNIFICANCE TO TABULAR DATA.

Time of Interval	No. Live Births Observed	Expected	Obs.-Expected $f_o - f$	$\frac{(f_o - f)^2}{f}$
12 M - 3 AM	4064	4028	36	0.3
3 AM - 6 AM	4627	"	599	89.0
6 AM - 9 AM	4488	"	460	52.5
9 AM - 12 N	4351	"	323	25.9
12 N - 3 PM	3262	"	-766	145.5
3 PM - 6 PM	3630	"	-398	39.3
6 PM - 9 PM	3577	"	-451	50.5
9 PM - 12 M	4225	"	197	9.6
Total	32224			$\chi^2 = 412.6$

$$\chi^2 = \Sigma\left(\frac{(f_o - f)^2}{f}\right)$$

For N = 7, P = $\ll .01$

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	Mean	S.D.	N (No. of Items in Sample)
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12 N - 3 PM	922	"	-756	142.5
3 PM - 6 PM	1930	"	-398	39.3
6 PM - 9 PM	1771	"	-451	50.5
9 PM - 12 M	1225	"	197	9.6
Total	12224			$\chi^2 = 412.6$

$$\chi^2 = \left\{\frac{(f_o - f)^2}{f}\right\}$$

For N = 7, P = <.01

Fig. 6. APPLICATION OF CHI SQUARE TEST TO FOURFOLD TABLE.

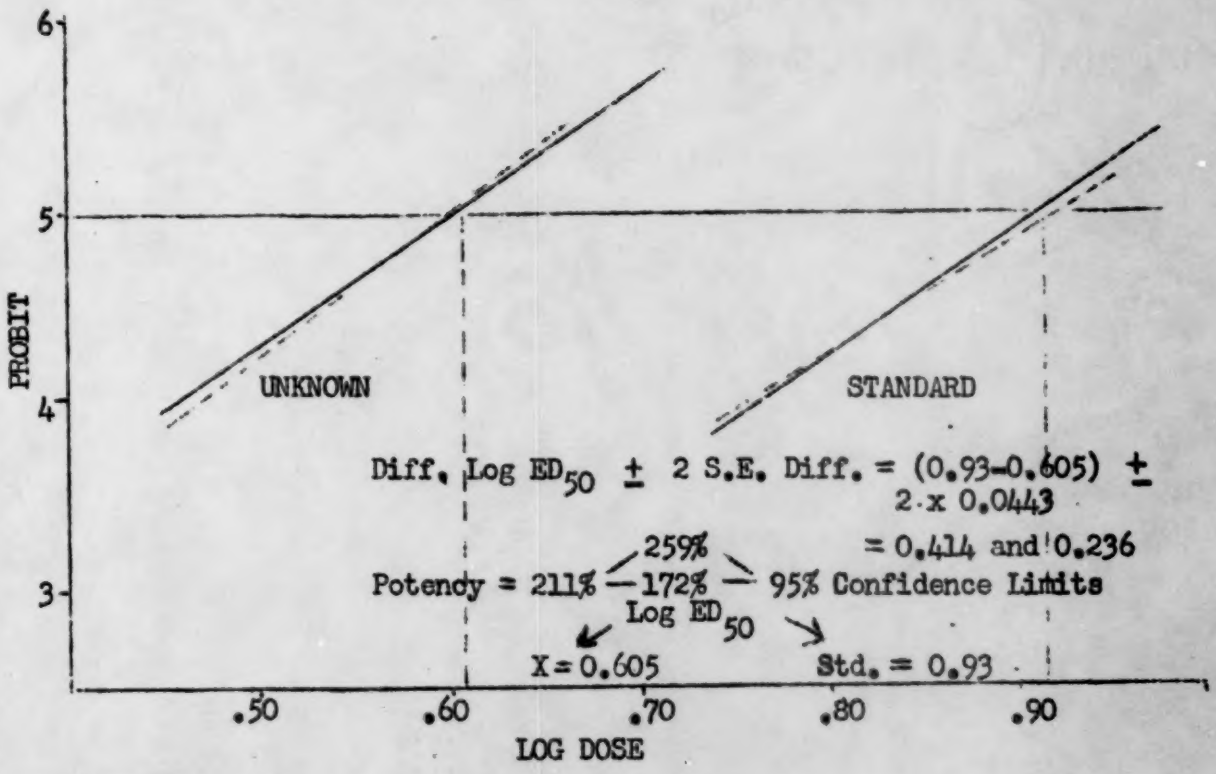
	No. Mice Alive	No. Mice Dead	Total
Treated	10 (a)	40 (c)	50 (a+c)
Untreated	5 (b)	45 (d)	50 (b+d)
Total	15 (a+b)	85 (c+d)	100 (a+b+c+d)

$$\chi^2 = \frac{(ad - bc - \frac{1}{2}(a+b+c+d)^2 \ (a+b+c+d)}{(a+b)\ (c+d)\ (a+c)\ (b+d)} = 1.255$$

where ad = greater cross-product

For N = 1, P = 0.2-0.3

Fig. 7. GRAPHICAL SOLUTION OF A QUANTAL ASSAY



b (slope) = 6.74

$\sigma = \frac{1}{b} = 0.1485$

$$S.E._b = \frac{4}{\sqrt{\frac{N^1}{2} L \frac{k}{k-1}}} = \frac{4}{\sqrt{\frac{45}{2} \times 0.2 \times \frac{3}{2}}} = 2.81$$

$$S.E._{\text{Log ED}_{50}} = \frac{\sigma}{\sqrt{\frac{N^1}{2}}} = \frac{0.1485}{\sqrt{\frac{45}{2}}} = 0.0313$$

$$S.E._{\text{Diff. Log. ED}_{50}} = \sqrt{\frac{\sigma^2}{N} + \frac{\sigma^2}{N}} = \sqrt{\frac{(0.1485)^2}{\frac{45}{2}} + \frac{(0.1485)^2}{\frac{45}{2}}} = 0.0443$$

FIG. 6. APPLICATION OF CHI SQUARE TEST TO POOLED TABLE.

	No. Alive	No. Dead	Total
Treated	10 (a)	40 (c)	50 (a + c)
Untreated	5 (b)	45 (d)	50 (b + d)
Total	15 (a + b)	85 (c + d)	100 (a + b + c + d)

$$\chi^2_1 = \frac{(ad - bc - \frac{1}{2}(a+b+c+d))^2 \ (a+b+c+d)}{(a+b)\ (c+d)\ (a+c)\ (b+d)} = 1.255$$

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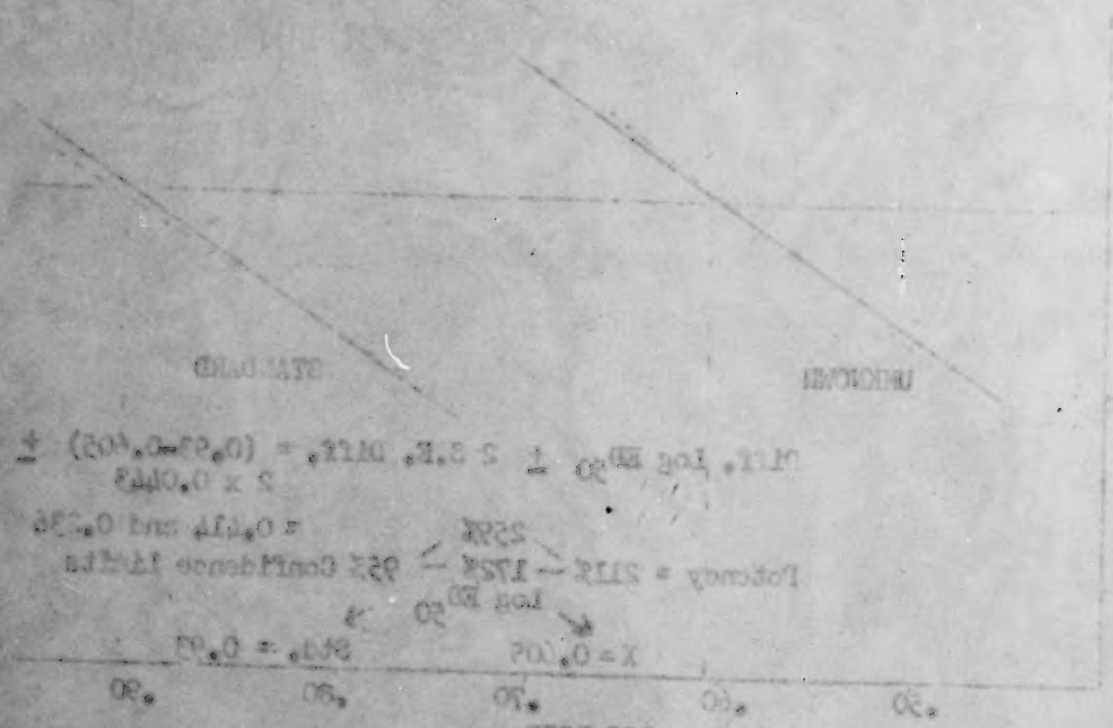

PLT. Log ED_{50} $\pm$ 2 S.E. DIFF. = $(0.97-0.405) \pm 2 \times 0.0443$

Potency = 21% — 172% — 95% Confidence limits

χ^2 = 0.414 and 0.736

$\log ED_{50}$

X = 0.105 SD = 0.93

S.E. $\log ED_{50} = \sqrt{\frac{pq}{n}} = \frac{d}{\sqrt{\frac{n}{2}} \times 0.2 \times \frac{1}{2}} = 2.83$

$C = \frac{b}{a} = 0.1485$

P (slope) = 6.71

S.E. $\log ED_{50} = \frac{d}{\sqrt{\frac{n}{2}}} = \frac{0.1485}{\sqrt{\frac{n}{2}}} = 0.0313$

S.E. Diff. Log. $ED_{50} = \sqrt{\frac{pq}{n} + \frac{pq}{n}} = \sqrt{\frac{(0.1485)^2}{\frac{n}{2}} + \frac{(0.1485)^2}{\frac{n}{2}}} = 0.0443$

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RADIOACTIVE TRACER TECHNICS IN TEACHING AND RESEARCH

John E. Christian, Professor of Pharmaceutical
Chemistry and Coordinator of Bio-nucleonics Research
School of Pharmacy, Purdue University
Lafayette, Indiana

In introducing my discussion of radioactive isotopes, I want, first of all, to have you keep in mind that the progress of science is characterized by the discovery and use of relatively few instruments having outstanding application in the progress of research endeavor. The analytical balance and microscope are examples of such instruments.

Within recent years (the last fifteen to be more precise) two very important instruments falling into the category of outstanding instruments of research have been developed. The first of these is the cyclotron and allied instruments such as the betatron, synchotron, linear accelerator, etc. The second is the chain reacting nuclear pile. The cyclotron and allied instruments being used for the production and study of high speed particles of various description, and the pile for the production and study of slow neutrons in high flux.

These instruments are important not only from the standpoint of their use in theoretical studies, but also in the production of radioactive isotopes which in turn serve as outstanding tools of research.

The present indications are that the range of usefulness of radioactive isotopes as research tools is unsurpassed by any other tools at our disposal with the possible exception of the microscope and the balance.

The apparent peacetime applications of particle accelerators and the pile may be classified under three general headings:

1. The pursuit of fundamental atomic research, leading without question to further constructive applications of isotopes and certainly to advances in human knowledge. There is still much to be known about the fundamental particles of matter and about the nucleus of the atom—additional knowledge means additional applications yet undreamed of.

2. The development of useful power, leading to economical and sociological gains. If the raw material were available for peacetime use, such power would be of economic importance today and would compete with other sources of power in certain areas of the world.

3. The production of radioactive products and their use in industry, medicine and research, leading to increased knowledge and beneficial applications in a wide range of scientific, industrial and medical fields.

This latter use, the production of radioactive products, is the one in which we are primarily concerned, but the overall perspective of utilization is essential in thinking of specific applications to a specific area such as pharmacology.

There are two important general classes of the use of radioactive isotopes, both of which depend on the ability of such isotopes to liberate

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ionizing radiation. These are (1) as sources of ionizing radiation and (2) as tracer substances.

As examples of the use of isotopes as sources of ionizing radiation, eight uses are listed:

1. Therapeutic and diagnostic agents
2. Well logging
3. Thickness gauges and control
4. Static electricity eliminators
5. Liquid level measurement
6. Fluid flow studies
7. Preparation of radiographs
8. Ionizing effects on tissue

There are many more applications; however, these convey the general idea of such applications.

By far the most productive and certainly the most interesting to the pharmacologist at least, is the use of isotopes as tracer substances, the use of which offers distinct advantages. Radioisotopes permit the tracing of elements, molecules, particles, or bulk material with the ultimate in (1) specificity, (2) sensitivity of detection and (3) attention to complexity of details. Since a radioactive isotope behaves identically with the other isotopes of the element in chemical and physiological processes, it labels without question the particular atoms one wishes to trace regardless of what happens to the atoms in complex systems. This specificity of the label is even greater than the detection of a species of atom. One can trace a particular batch of a certain kind of atom. For example, one can label the calcium atoms in a glass of milk and at any time later distinguish these calcium atoms from those already present in the body or those taken into subsequent food. The actions of a particular group of sodium atoms can be distinguished from the actions of those already in the body, etc. So the specificity of isotopic labels is the ultimate.

The sensitivity of detection of radioactive isotopes is phenominal, being up to one million times as sensitive as any other method known. Less than 100,000 atoms or roughly 10^{-18} to 10^{-19} grams can often be detected. So the sensitivity of detection is the ultimate.

The complexity of processes traceable with radioactive isotopes is almost unlimited. Labeled atoms can be traced through a labyrinth of reactions and systems; for example, labeled atoms may be traced from fertilizer to the plant, from plant to animal and from animal to man. Atoms may be traced from carbon dioxide to glucose, from glucose to fat, etc. Microorganisms and insects can be labeled and followed wherever they go. So the attention to the complexity of details is also the ultimate.

Radioactive isotopes in quantity have been available for about four years. During the past year to a year and a half the number and availability of isotopes has increased considerably. Along with this the cost has decreased, in some instances by large amounts. There are over 700 radioactive isotopes which have been characterized and over 110 of these are available in quantity. The ones which have been made the most readily available are the ones of most importance in biological research. The following table lists a few of the important radioactive isotopes for

ionizing radiation. These are (1) as sources of ionizing radiation and (2) as tracer substances.

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biological use.

Important Radioactive Isotopes

Isotope	Half-Life	Cost/mc.*
Carbon - 14	5,740 years	$ 36.00
Phosphorus - 32	14.3 days	1.10
Sulfur - 35	87 days	1.00
Calcium - 45	180 days	2.00
Iron - 59	46.3 days	35.00
Cobalt - 60	5.2 years	2.00
Iodine - 131	8 days	0.75
Mercury - 203	43.5 days	1.00
Sodium - 24	14.8 hours	0.80
Sodium - 22	2.6 years	100.00

*A ten dollar handling fee and the shipping cost must be added to the cost of the isotope to arrive at the total cost.

The present big bottleneck in the use of the available isotopes is the synthesis of the desired labeled compounds with appropriate atoms in appropriate positions in the molecule. However, this situation is improving since a rapidly increasing number of labeled compounds are becoming available. In January 1948, Methanol-1-C^{14} was the only labeled compound available for sale. In January 1949, two dozen such items were available. In January 1950, over 130 were available and in January 1951, over 300 were available. All of these have been made available through chemical synthesis. Over fifty labeled compounds have now been prepared by biological synthesis. The bulk of both the chemically and biologically produced compounds are carbon-14 labeled; however, some are labeled with iodine-131, sulfur-35, phosphorus-32, and cobalt-60.

This covers the general considerations of isotope utilization in research and industry which brings us to a brief discussion of some of the specific applications to the area of pharmacology. There is little question about the importance of radioactive tracer techniques in studying the rate of absorption, excretion, metabolic products, distribution and mechanism of pharmacological action of medicinal substances as well as toxic and other materials normally taken into the body. Previous speakers at this seminar have emphasized the importance of making such studies. The point that small doses of drugs may give large effects and that in most cases drug action is a series of chemical events in cell metabolism about which much is yet to be learned has been stressed. Radioactive isotopes offer a new and in many instances a surprisingly simple approach to answering these problems. Such studies have already caused the discarding of some of the older theories of drug action and concentrations. Newer theories based on recent studies have been postulated but in general the indications are that the actions are much more complex than originally thought.

Isotope tracer studies have already been made on a number of medicinals such as the barbiturates, sulfa drugs, thyroid drugs, amino acids, vitamins, carcinogens, estrogens, antibiotics, etc. The possibilities of determining the breakdown products alone, using tracer techniques will

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unquestionably be of extreme value in postulating new and in many cases simpler structures having comparable action.

By the use of the radioautographic technique for the determination of distribution, the carrier technique for qualitative studies, and the direct and inverse isotope dilution techniques along with induction analysis for quantitative studies more detailed studies can be made, even where the concentrations are extremely minute.

The possibilities for the use of radioactive isotopes for the pharmacological testing of medicinal and toxic substances are apparent. The determination of blood and plasma volume, circulation time, restricted blood circulation, pumping qualities of the heart, and of thyroid function are examples of such utilization.

In pharmacological studies of the elements themselves the use of radioactive isotopes presents many interesting possibilities. Good examples of this type of use are the very excellent work which has been done with iron-59 and sodium-24 in studying absorption, distribution, excretion, concentration, etc. of these elements.

The examples presented are but a few of the possibilities which are apparent for use in pharmacological procedures. There are still tremendous numbers of yet undreamed of possibilities which will become apparent as this new tool finds more extensive utilization.

In conclusion, it should be pointed out that isotopes in quantity and at low cost have been available only during the last four years. In these four years tremendous growth of application has occurred even though several obstacles to their full use have been in the path of such utilization. Many of these obstacles are being rapidly dissipated. Scientific persons are rapidly losing their fear of the use of isotopes. Well trained personnel who understand the advantages as well as the limitations are being trained. Basic data, equipment and methods have been adequately developed to a point where little time need be lost in using isotopes as research tools. Finally, tagged compounds and elements are becoming more and more available and cheaper.

After careful consideration of these factors along with certain others, one is easily convinced that within the next 10 to 15 years radioactive isotopes will be as common place in pharmacological laboratories and used to as great an extent as many of the research tools commonly used today.

Sound advice to pharmacologists, both in industry and teaching, is to look ahead ten years and start now to build for the use of radioactive isotopes as research tools.

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APPLICATIONS OF PHARMACOLOGY TO ANIMAL SCIENCE

F. N. Andrews
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The scope of pharmacology is so broad that there should be little surprise, even to pharmacologists, at the many applications of the science. There seems to be a logical basis for the classification of all substances as drugs. Such a classification seems to infringe upon the chemist, the physicist or even the butcher or grocer and we have sometimes attempted to solve such jurisdictional disputes by resorting to functions or uses of the substances in question. Such a procedure is not without hazards. Whereas the pharmacologist is inclined to regard alcohol as a stimulant or depressant, it may be a sterilizing agent to the microbiologist, a dehydrating substance to the histologist or a sure-fire seller to the distiller.

In recent years many unsuspected uses for standard drugs and new chemical substances have developed. It was not surprising that antibiotics such as penicillin, streptomycin, aureomycin and others developed for the control of human diseases should be equally effective in the treatment of animal diseases. It was, however, very surprising even to the initiate that the addition of certain antibiotics to animal feedstuffs would greatly increase the rate of growth of farm animals. It was not surprising that stilbestrol, a synthetic female-like sex hormone would alleviate many of the menopausal symptoms of the human; it was surprising that the injection of minute quantities of stilbestrol would increase growth and the efficiency of feed utilization in cattle and sheep. It was probably surprising to all concerned that thiourea, a compound used in photographic fixing agents and in the manufacture of resins, should prove to inhibit the utilization of iodine by the thyroid gland. Many similar examples could be chosen. The writer will discuss only a few which are involved in the practical utilization of hormones in farm animal production.

It has long been known that such important body functions as growth, reproduction, lactation and the fattening process are either directly or indirectly controlled by the endocrine or ductless glands. These glands secrete specific chemical substances called hormones.

From the standpoint of practical livestock production the hormones which are of most interest to us at the moment are those of the anterior pituitary, thyroid, adrenal and sex glands (ovaries and testes).

The Estrogens

There is a great number of naturally occurring and synthetic female sex hormones. These substances are extremely widespread. They are normally produced by the ovaries, but may be present in significant amounts in sources such as grasses, legumes, molds, petroleum and various body secretions. Most of the naturally occurring estrogens can be prepared synthetically. There is, however, a great difference in the cost of synthetics.

Among the synthetics which are readily available is stilbestrol. It does not occur naturally in the body, but when administered to animals

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Among the synthetics which are readily available is stilbestrol. It does not occur naturally in the body, but when administered to animals

or humans it can substitute rather effectively for the natural ovarian hormones. Stilbestrol has the advantage of being low in cost. In human medicine stilbestrol is used to make the menopausal transition smoother. In veterinary medicine it is widely used to induce heat in sexually inactive females and to treat various disorders of the reproductive organs.

Jaap, Lorenz and others have clearly showed during the past decade that the injection or feeding of stilbestrol and other estrogens will increase fattening and improve market quality in chickens and turkeys. The effects in broilers are so striking that injections of stilbestrol in various forms is now a standard practice in poultry production. The use of stilbestrol pellets has been approved in the United States by the Pure Food and Drug Administration. The feeding of estrogens, however, has not yet been approved because there is not sufficient evidence that it can be done safely with the estrogens at present available. It is emphasized that in birds increased fat deposition is very apparent. In cattle and sheep the effects of stilbestrol appear to be a stimulation of rate of growth rather than an increase in fatty tissue.

During the past five years several experiments have been conducted at the Purdue University Agricultural Experiment Station on the effects of both the female and male sex hormones on the rate of growth of cattle and sheep.

Two experiments with beef heifers showed that stilbestrol increased the rate of gain and improved feed efficiency, The observation of two groups of beef heifers which had been injected with stilbestrol while grazing on lush pasture prompts the warning that excessive mammary growth may occur under such conditions.

Two trials with beef steers showed that rate of gain and efficiency of feed utilization may be greatly improved by both stilbestrol and a second synthetic estrogen, dienestrol. In a recent 140 day trial yearling steers on a ration of corn-and-cob meal, cottonseed meal, molasses feed, clover-timothy hay, bonemeal and salt gained at a rate of 2.56 lb. daily and required 782 lb. of concentrates per 100 lb. of gain. Steers in which 60 milligrams of stilbestrol pellets were injected beneath the skin in the neck gained 2.9 lb. daily; cattle receiving 120 milligrams of stilbestrol gained 3.0 lb. per day and those which received 80 milligrams of dienestrol gained 2.9 lb. daily. The hormone-treated steers required only 694 to 698 lb. of concentrates per 100 lb. of gain. In both experiments, carcass grades were higher in the control than in the treated cattle.

Experiments with castrate male lambs have shown that both stilbestrol and dienestrol increase rate of gain and improve feed efficiency. As in the case of beef cattle, carcass quality was somewhat reduced by estrogen treatment.

Thiouracil and other goitrogens.

Since 1942 a series of compounds which affect the activity of the thyroid gland have been developed. Since the thyroid gland is involved in growth, fattening and numerous other body functions it was hoped that these compounds might find practical application. The goitrogens depress thyroid activity and metabolic rate. Fat deposition tends to increase and

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Two trials with beef steers showed that rate of gain and efficiency of feed utilization may be greatly improved by both stilbestrol and a second synthetic estrogen, dienestrol. In a recent 140 day trial yearling steers on a ration of corn-and-cob meal, cottonseed meal, molasses feed, clover-timothy hay, bonemeal and salt gained at a rate of 2.56 lb. daily and required 782 lb. of concentrates per 100 lb. of gain. Steers in which 60 milligrams of stilbestrol pellets were injected beneath the skin in the neck gained 2.9 lb. daily; cattle receiving 120 milligrams of stilbestrol gained 3.0 lb. per day and those which received 80 milligrams of dienestrol gained 2.9 lb. daily. The hormone-treated steers required only 698 lb. of concentrates per 100 lb. of gain. In both experiments carcass grades were higher in the control than in the treated cattle.

Experiments with castrate male lambs have shown that both stilbestrol and dienestrol increase rate of gain and improve feed efficiency. As in the case of beef cattle, carcass quality was somewhat reduced by estrogen treatment.

Thiouracil and other goitrogens.

Since 1942 a series of compounds which affect the activity of the thyroid gland have been developed. Since the thyroid gland is involved in growth, fattening and numerous other body functions it was hoped that these compounds might find practical application. The goitrogens depress thyroid activity and metabolic rate. Fat deposition tends to increase and

feed requirements are reduced. Unfortunately rate of growth declines. Since rapid growth is essential in meat animals the decline in growth rate is a serious limitation. At the present time the only possible practical application has been during the last few weeks of fattening in swine.

Thyroprotein

One of the best known of all supplementary hormone sources is thyroprotein. Thyroprotein is the descriptive name of proteins to which iodine has been bound in such a way that compounds similar to the naturally occurring thyroid hormone are formed.

The greater part of commercial thyroprotein is used for the stimulation of milk production in dairy cattle. It has been known for almost 20 years that thyroxine administered to cows in the declining phase of lactation will stimulate milk production. It appears that in some cows natural deficiencies in the activity of the thyroid gland limit milk production.

There are at least two problems involved in the practical use of thyroprotein in dairy cattle. Most cows receiving proper amounts of thyroprotein do increase in production. However, some cows respond much more favorably than others and some may not tolerate thyroprotein. The dairyman using thyroprotein must be able to evaluate the response. The second problem is an economic one. Cows receiving thyroprotein require more feed. If the increased milk flow does not pay for the cost of the material and increased feed it is obvious that the use is not economic.

Some experiments have shown that thyroprotein will stimulate growth in swine. Thus far it has been difficult to control the response. Until satisfactory techniques can be worked out the material will have limited use.

The addition of thyroprotein to the rations of young chicks has been shown to accelerate feathering.

Human health aspects

When drugs of any sort, whether they be in the nature of vitamins, hormones, antibiotics, insecticides or of other nature, are administered to meat, milk or egg producing animals it is necessary that they have no harmful effects on the humans consuming such products.

Stilbestrol can be used for the stimulation of growth and fattening in poultry in the United States provided it is administered in pellet form in the neck region. In Canada, on the other hand, such use is not permitted. At the time of writing, stilbestrol has not yet been approved for purposes of stimulating growth in sheep or cattle.

The use of thyroprotein for the stimulation of milk production in dairy cattle, and for inclusion in swine and poultry rations appears to have no undesirable effects on the products produced. To the author's knowledge, there has been no official opinion as to the acceptability of thiouracil or other goitrogens for inclusion in the rations of meat

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animals. The best evidence available seems to indicate that thiouracil disappears from the tissues of meat animals very shortly after its use in the ration is discontinued.

The effects of drugs in the treatment of animal diseases could be discussed in great length. Veterinary medicine and veterinary pharmacology are very similar to human medicine with the possible exception of emphasis. Whereas the alleviation or prevention of suffering takes precedence in man, the economic relationship of healthy animals in fulfilling man's material needs looms largest in animal applications.

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GRADUATE INSTRUCTION (A PANEL DISCUSSION)

Objectives of Graduate Training in Pharmacology by Harold W. Werner

The primary objective of graduate training in pharmacology should be to develop individuals who are capable of recognizing problems and solving these problems in an economical way.

This means that the training must aim to develop the individual along three lines.

First, it must provide an adequate background of technical information and skill. Emphasis here should be placed on fundamentals and correlations rather than on simple learning of isolated facts.

Second, the training must aim to develop research ability. Emphasis here should be placed on recognition and understanding of problems, organization of plans of attack, execution of the plans, and drawing of sound conclusions.

Third, the training must aim to develop certain qualities or traits of character which are characteristic of the well-rounded individual and are important in research and other functions.

There are many of these qualities, and their importance is appreciated almost as soon as they are mentioned.

Intellectual honesty and objectivism are of fundamental importance in any scientific work. This is true because research work is primarily concerned with the discovering of facts, and facts by definition cannot be colored by personal preferences and feelings.

Every effort should be made to develop an active, inquiring, and interested mind. Active interest and curiosity are essential to the recognition of major problems and voids of information. These characteristics are necessary also for the recognition of problems and difficulties arising daily--problems which call for modification of technics or approaches if research is to be successful. Active interest and curiosity are important elements also in the making of unexpected or unplanned discoveries.

Judgment and intelligent discrimination also must be developed. These qualities are essential for the determination of the relative importance of both small and large problems. Along with technical information and skill they are necessary for the most economical solving of problems, and they are essential to the drawing of sound conclusions.

Patience and perseverance need to be developed. Few pieces of research, or for that matter few jobs of any nature, can be brought to a successful conclusion without these virtues. Yet the individual must learn to temper his tenacity with judgment or he may blindly pursue an objective which can never be attained or attained only at too high a cost.

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The abilities to talk well, write, get along with people, and administer are needed to various degrees in different jobs, but all are becoming more important in the functioning of our present-day organizations.

Originality, imagination, and idea ability are the extra plus qualities. They are the ones which lead to creative ability and unusual accomplishment. Probably originality cannot be modified greatly in graduate training, but imagination and ideal ability can be improved.

Finally, the graduate student should appreciate the importance of industry and enthusiasm for work. Ideally these qualities are fairly well developed before graduate work is started. Practically improvement may be necessary, but it should come easily as other aims of the program are attained.

Graduate Instruction in Pharmacology--Qualifications of Staff and Students

by
Ewart A. Swinyard

Graduate study in pharmacy is offered in five major fields of specialization, namely, pharmacy, pharmaceutical chemistry, pharmaceutical administration, pharmacognosy, and pharmacology. Advanced degrees in the first four fields can be obtained only in colleges of pharmacy. As a result, the objectives are fairly uniform, although the quality of such training may vary considerably depending primarily upon the ability and ingenuity of the man who directs the program. On the other hand, advanced degrees in pharmacology may be obtained either in a college of pharmacy or a college of medicine. This at once imposes an unusual responsibility on the colleges of pharmacy that presume to offer graduate instruction in pharmacology. There are certain differences in the objectives of graduate training in pharmacology offered in colleges of pharmacy and in colleges of medicine, nevertheless, these objectives are sufficiently similar so that only that college of pharmacy which can offer work comparable with that offered in a college of medicine should attempt to offer the doctorate degree in pharmacology. It should be remembered that pharmacology was originally fostered by the medical schools and presumably should have attained its highest level of academic excellence in these institutions. Unfortunately, this view is not uniformly accepted. Irrespective of this opinion, unless the graduate who has been trained in pharmacology in a college of pharmacy has an education at least equal to that of the medical school trained man he will find himself seriously handicapped when it comes to securing one of the better positions in industry, food and drug administration laboratories, research foundations or educational institutions. In the writer's opinion, there are but very few departments of pharmacology in pharmacy colleges that are prepared at present to offer the Ph. D. degree. For the benefit of other schools it is of interest to note here the necessary minimum qualifications of staff and students for a creditable graduate program in pharmacology.

Qualifications of the Staff

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Qualifications of the Staff

In general, the same rigorous requirements concerning staff should apply to the department of pharmacology which plans to offer graduate

instruction in pharmacology as apply to the various divisions of a Graduate School in our better universities. The biggest hurdle, therefore, is the number of staff members in the department. Rarely, if ever, is a department permitted to offer graduate instruction to the Ph.D. if there is only one professor in that department. It is realized that such a requirement of multiple staff members will automatically exclude the vast majority of colleges of pharmacy from graduate instruction in pharmacology. However, under certain circumstances, a department which has only one or two staff members may undertake graduate instruction. Such circumstances would obtain when the college of pharmacy is closely allied with an active university graduate school in which graduate courses in biochemistry, physiology and other ancillary fields are offered.

The faculty member directly responsible for graduate instruction in pharmacology must have a doctorate degree in pharmacology and must have published sufficient meritorious independent research to enjoy the full confidence of his colleagues. Indeed, he must be actively engaged in research.

The faculty of a college of pharmacy offering graduate instruction in pharmacology must be "strong" in the sense that its members are recognized for their research contributions in their respective fields. Such recognition can only be gained if the faculty members do fundamental research and are active in their respective professional societies.

Qualifications of students. Admission to graduate work in pharmacology should be granted only to graduates of accredited colleges of pharmacy. Undergraduate training should include, -- in addition to the usual courses in pharmacy, pharmacognosy and pharmaceutical chemistry, -- inorganic, organic, qualitative and quantitative chemistry, physics, biology, bacteriology, and physiology, and, a year's course in pharmacology. In addition, the student should have courses in mathematics through the calculus, or should complete these during his graduate work.

The general ability of the graduate student is, to a large extent, reflected in his scholastic record. The scholastic record may be used as an indication of his intelligence, memory, industry and general interest in education. However, other qualifications, such as a sincere interest in pharmacology, judgment, ability to read and interpret the scientific literature, and manual dexterity, should be taken into consideration. In addition, the graduate student should have the necessary physical and mental stamina to enable him to make the necessary adjustments to graduate work and to withstand the long hours of work and study required for the doctor of philosophy degree. Some of these qualities can be determined by personal interview, by a graduate record examination, and by previous experience with the applicant. Finally, the student who presents all of these qualifications should only be accepted for graduate study with the realization that all professional careers in pharmacology are concerned with research and that the lifetime occupation of all candidates for the doctor of philosophy degree in this field involves original investigation irrespective of the specific position finally accepted.

Choice of Problem by Carl A. Bundy

Same general principles as would influence choice of problem in any graduate school.

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Choice of Problem by Carl A. Brandy

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Be sure that the chief reason for choice is the value of the problem to provide instruction and learning.

School and research laboratory do not always have identical aims. The problem should fit the aims of teaching even though this does not contribute most to the professor's research program.

Problem should be related to a financial grant only if that grant supports a good teaching problem. A graduate student should not be made a technician just to get the professor's work done or just to qualify for a grant.

Definition of a good teaching problem:

1. Must be within the scope of the student's ability and time.
2. Must employ a variety of classical techniques.
3. Must have sufficient evident importance to be stimulating.

Graduate Courses in Pharmacology by Leroy D. Edwards

It is the opinion of the writer that the program of courses offered for pharmacological graduate study should include some instruction in every basic phase of that field. This approach seems logical for the following reasons:

(1) Pharmacology can be subdivided into several sharply defined areas, i.e., routine bioassays, screening of new compounds for drug action, toxicology, pure pharmacology including mechanism of action and a correlation of chemical structure and response, product development, teaching, etc.

(2) There appears to be a tendency to specialize these areas.

(3) The graduate in most instances has no way of determining in which specialized area he will operate upon graduation.

(4) If the student is familiar with the basic principles he can effect a high degree of specialization in an area through self-education after graduation. Thus, assuming that the student has had or will take all essential prerequisite and supplementary courses, the graduate courses in pharmacology should include the following: (a) Advanced pharmacology, (b) Experimental animal surgery, (c) Bioassays, (d) Drug screening, and (e) Toxicology.

Advanced Pharmacology

The approach in this course may well be from the standpoint of cellular pharmacology, and, then with this foundation, tissue and organ pharmacology may be developed. Finally, the effects of drugs on the several systems of the intact animal should be studied. The mechanism of action and the correlation of chemical structure to response should be emphasized wherever possible. Laboratory work should be arranged to illustrate the type methods employed in such studies.

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Experimental Animal Surgery

This course should consist of the more complex surgical techniques and practices met in the use of the larger animals such as the dog in pharmacological experimentation. These several techniques and practices are well described in the textbook of Experimental Surgery by Markowits, Williams and Wilkins.

Bioassays

Here the fundamentals of bioassay procedures including statistical analysis of results should be covered. The official bioassays should receive first consideration in the laboratory phase of the course. Biological Standardization by J. H. Burn, Oxford University Press, 1950, is illustrative of the material which should be included in this course.

Drug Screening

A general screening routine should be presented. In the laboratory, the student should obtain familiarity with these techniques using known drugs. Unknowns may then be used to test the progress of the student.

Toxicology

The objective in this area should be to acquaint the student with the procedures used in the isolation of poisons from organic material and the means of identification of these poisons after isolation. In some instances as arsenic, alcohol, etc., it will be necessary to employ quantitative methods. The use of "unknowns" is very instructive. Type material for a course of this kind is to be found in Clinical Toxicology by Thienes and Haley, 1948, Lea and Febiger, Philadelphia.

In addition to the above five basic courses in graduate instruction in pharmacology, a Special Problems course and, certainly, a Seminar in Pharmacology are most productive.

These courses as outlined would easily satisfy a major in pharmacology for the Ph. D. degree. The supplementary courses could be used for such minors as physiology, bacteriology, pharmaceutical chemistry, pharmacognosy, pharmacy, organic chemistry, etc.

The Graduate Seminar by Frank T. Maher

Seminars with graduate college recognition are frequently combined with, or presented as, staff seminars. It is our purpose here to stress the particular aims of the seminar directed to the graduate student.

The graduate seminar centers around the training of the graduate students (a) majoring in the field; (b) doing a minor; and (c) from other fields, seeking correlative information. It is thus an integral part of the graduate teaching program. It should not be designed to replace or supplant formal course instruction at graduate levels.

Seminar programs should be varied to provide:

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2. Recognized investigators, presenting progress reports on research activities in specific areas.

3. Workers in associated and supporting fields of study, bringing a summary of outstanding progress in related areas.

4. Brief descriptions of research and teaching programs by other local departments, and by other students within the department—seeking to orient the student in the totality of effort within the institution.

5. Opportunity for each graduate student to appear before the group for oral presentation of:

   (a) Progress reports of research projects.
   (b) Final description of completed work.
   (c) Library research on assigned topic.

6. Review and discussion of methods and practices of scientific writing, thesis development, and oral presentation.

Each program should provide time for a thoughtful consideration of material presented, and a general discussion by graduate students and staff. Designating in advance one or two commentators who serve to open discussion has been effective in our experience. Graduate students should be encouraged to enter freely into these discussions.

For the past three years we have maintained at the University of Illinois a "General Pharmacy Seminar," in addition to departmental seminars in biology, chemistry and professional pharmacy. Topics presented are basic in nature, but slanted toward a problem in pharmacy. General topics are divided in presentation among several areas of thought; graduate students present active and completed research before a critical audience of varied representation. This type of program has frequently served to orient the graduate student, to correct experimental design or approach with economy of time and facilities.

With a wide field from which to formulate seminar programs, the stress upon the graduate seminar as predominently an educational experience must be maintained. This objective is best approached by considering each item in the total program, and its presentation, from the viewpoint of its value in forwarding the course of graduate education.

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AN ELEMENTARY COURSE IN TOXICOLOGY

C. W. Muehlberger, Toxicologist
Michigan Dept. of Health
Lansing, Michigan

Inasmuch as I have never had the opportunity of teaching in a school of pharmacy, it is presumptuous on my part to come before you and attempt to discuss the teaching of toxicology in a pharmacy course. I can, however, recount to you the experiences which we have had in the teaching of toxicology to medical students. The program which I will outline was developed very largely at the University of Chicago under the leadership of Dr. E. M. K. Geiling, Chairman of the Department of Pharmacology. The courses consisted of a series of about 13 to 16 lectures and an optional laboratory course covering about 8 afternoon laboratory periods.

Lecture Course

Where time permits, it seems desirable to open the lecture course with an illustrated lecture on "The History of Poisoning". Following this, the definition of the term "poison" should be discussed, in order to delineate the field which is to be covered. The general pharmacological principles involved in the toxic action of substances is much the same as those governing the beneficial action of medicinal drugs, so that these may be rapidly gone over. The avenues of absorption of toxic substances are discussed, also the rate of absorption through these various avenues and factors which alter the rate of absorption. The distribution and elimination of the toxic substances is then discussed, including the mechanism of elimination either by hydrolysis, oxidation, conjugation, ester formation or simple excretion. The avenues of elimination are outlined and factors which influence the rate of elimination are discussed. Cumulative action of toxic substances leading to chronic poisoning are also detailed and a discussion of tolerance and idiosyncrasy is included, particularly with reference to poisoning.

Because the pharmacist is, in many instances, close at hand in acute poisoning cases, he should have knowledge concerning emergency treatment of poisoning, even though the handling of the case can best be left to the direction of medically-trained persons. Principles of treating a case of poisoning are therefore gone into. These consist of (1) Prevention of further absorption of poison, either by producing vomiting, resorting to gastric lavage or judicious use of antidotes for poison which has been swallowed. It should be borne in mind that the stomach is not a glass beaker or test tube and that powerful antidotes are definitely contraindicated. Thus one should administer vinegar in cases where caustic alkalies have been swallowed or milk of magnesia where powerful acids have been taken. Lloyd's Reagent is an excellent adsorbant for swallowed alkaloids. (2) Treat the effects of the poison which has already been absorbed. This should be done under medical supervision and consists in the injection of specific antidotes, such as soluble barbiturate for strychnine poisoning, picrotoxin for barbiturate poisoning, sodium thiosulfate and sodium nitrite in cyanide poisoning and BAL for most acute metallic poisons. (3) Give supportive treatment by maintaining body temperature, giving artificial respiration where indicated or by employing cardiac stimulants where there is circulatory depression.

AN ELEMENTARY COURSE IN TOXICOLOGY

C. W. Muehlberger, Toxicologist
Michigan Dept. of Health
Lansing, Michigan

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After these generalized discussions, it is wise to pass on to the discussion of specific groups of poisons. Many of these which are common medicinal drugs can very well be discussed in the pharmacology course where their therapeutic action is under consideration. Thus arsenic and mercury compounds, strychnine, morphine, etc. may have their toxicity discussed at the point where these substances are under consideration in the regular pharmacology course. The lectures cover gaseous poisons (with considerable emphasis placed on carbon monoxide because of its common occurrence) caustic or corrosive poisons, including powerful mineral acids, caustic alkalies and phenols, discussion of the alcohols (with special reference to methyl and ethyl alcohol poisoning) discussion of cyanides, toxic metals and metalloids, toxic hydrocarbons, particularly of the aromatic series, chlorinated hydrocarbons and other toxic industrial solvents, hypnotic drugs, chiefly chloral and the barbiturate series, alkaloids.

In presenting these subjects it seems advisable to use demonstrations and visual aids to a limited extent. Thus where quick-acting poisons are under discussion, the toxic action and suitable antidotal treatment can be demonstrated in experimental animals before the class. In instances where the acute symptoms are striking and characteristic, movies of such animal experiments may be shown and to demonstrate the pathological conditions resulting from toxic action, lantern slides (particularly Kodachrome slides) may be shown. A few short "quiz" periods may be advisable through the lecture series. Quizzes should outline practical poisoning situations and invite the student's consideration concerning diagnosis (both physical and chemical), proper treatment and probable prognosis.

There are two schools of thought concerning educational technique in which the supplying of mimeographed notes is under controversy. One school adheres to the belief that requiring a student to take elaborate notes and to summarize the material presented in the lectures is the best way of fixing these in the student's mind. The other school, to which I am more inclined, believe that the maximum value can be obtained if the student is relieved of an attempt at taking shorthand notes and permitted to listen to the lecturer. Thus the student is permitted to devote himself wholeheartedly to the lecturer's presentation with the knowledge that the essential facts will be found in the mimeographed notes.

Laboratory Course (optional)

The laboratory course consists of a combination of demonstrations and chemical analyses (chiefly qualitative) to illustrate the action of poisons, the treatment of poisoning and the detection of the more common poisons. At each laboratory period a demonstration of the toxic effect of some poisonous substances in experimental animals is conducted and a different group of about four students is assigned to the demonstration for each laboratory period.

First laboratory period experiment consists in gassing animals in a gas chamber using carbon monoxide, also demonstrating the effectiveness of oxygen therapy. Laboratory period, check over laboratory equipment and prepare special reagents.

Second laboratory period involves the testing of blood of animals

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poisoned in the preceding period to detect carbon monoxide-hemoglobin, both by chemical and spectroscopic means. The experiment for the second period consists in poisoning animals with cyanide and demonstrating the antidotal effects of sodium thiosulfate and sodium nitrite.

Third laboratory period, students test stomach contents, tissues and blood of animals poisoned with cyanide during the previous session, and as a laboratory demonstration further animals are poisoned with stomach administrations of alcohol and chloral hydrate.

Fourth laboratory period, blood, urine and tissues of animals previously poisoned with alcohol and chloral are tested and further animals are poisoned with inorganic arsenic and mercury preparations. The effectiveness of BAL as an antidote is demonstrated.

Fifth laboratory period, tissues of animals poisoned with arsenic and mercury are tested qualitatively for these poisons. Further animals are poisoned with barbital sodium and the use of picrotoxin as an antidote is demonstrated.

Sixth laboratory period, devoted to the extraction of barbital from liver, kidney and urine of animals previously poisoned. The laboratory demonstration consists in poisoning animals with strychnine administered by stomach tube and demonstrating the effectiveness of Lloyd's Reagent administered by mouth as an antidote.

Seventh laboratory period consists in testing stomach contents of previously poisoned animals for the presence of strychnine. Laboratory animals are poisoned with sodium fluoride and white phosphorus preparations.

Eighth laboratory period is taken up with qualitative tests of stomach contents of previously poisoned animals with fluoride and phosphorus.

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THE COMMON GROUND OF HUMAN AND ANIMAL DISEASES

L. M. Hutchings
Head, Department of Veterinary Science
Purdue University
Lafayette, Ind.

If one should feel the need of justifying an approach to the subject "The Common Ground of Human and Animal Diseases", he need but to consult the dictionary for definitions of man and animal. An animal, as distinguished from a plant, is any member of the group of living beings typically endowed with sensation and voluntary motion. Technically, an animal is an organized living being distinguished by possessing in greater or less degree the characters or attributes of sensation, of voluntary movement, of receiving and digesting solid food in an internal cavity previous to its absorption into the tissues and of having the katabolic processes of the cells paramount to the anabolic processes, so that oxygen is absorbed and carbon dioxide evolved during the life of the organism. Man is a human being; an individual of the genus Homo. Man is the highest type of animal existing or known to have existed, but differs from other animals more in extraordinary mental development than in anatomical structure.

Disease has been defined as an alteration in the state of the body or of some of its organs, interrupting or disturbing the performance of the vital functions. Thus it can be readily understood that there is a common ground for animal and human diseases. This paper will deal only with some of the diseases of animals which are transmissible to man rather than the whole array of abnormalities which have a common medium in man or animal. Suffice it to say that nutritionally, physiologically and anatomically there are common abnormalities of both man and animal.

Of the 83 or more diseases of animals which have been reported as being transmitted to man, the effects are measured ordinarily in terms of direct public health importance. Another viewpoint worthy of thought concerns the indirect importance of animal diseases in general on the economics of mankind. In other words, the diseases which animals have and do not transmit to man are of interest not only to the veterinarian, the physician, the research worker and the health official, but also to the economist. As Edward Jenner said in 1796, "The deviation of man from the state in which he was placed by nature seems to have proven to him a prolific source of diseases. From the love of splendour, from the indulgences of luxury, and from his fondness of amusement, he has familiarized himself with a great number of animals, which may not originally have been intended for his associates." This could well have been expanded to include man's dependence on animals for a living, for maintenance of soil fertility, and for their contribution to medicine. Such diseases as hog cholera, foot-and-mouth disease of cattle, Texas cattle fever, infectious bronchitis and pullorum disease of chickens, none of which are transmitted to man, have a profound indirect influence on man through the economic losses they produce. During certain years hog cholera in the United States has been conservatively estimated as causing 65 million dollars' loss. In ordinary years including the cost of prophylactic measures a 30-50 million dollar annual loss is recorded. Cattle tick fever or Texas cattle fever at the turn of the century was estimated to be taking an annual 40 million dollar toll from the South.

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Eradication of this disease has and is permitting a change from the cotton and sugar cane economy of the Deep South to one of diversified livestock farming. Similar estimates on other diseases have resulted in greater or lesser animal loss figures.

Currently, we hear a great deal about conservation of national resources. Such important factors as the development of hybrid corn, better land utilization, better use of fertilizer and conservation of water are all mentioned in our conservation programs. A less publicized portion of this whole picture is the improved management, nutrition and disease control in our domestic animals and poultry. It is a matter of record that Malthus in the 17th century predicted human starvation as the direct result of population increases. In this prediction he failed to consider or foresee many important technological developments which have tended to at least delay, if not overcome, the world shortage of food resulting from the increased population. In the animal field alone, the development of a satisfactory hog cholera vaccination procedure, the control of anemia in baby pigs, the control of rickets in chickens, better knowledge of parasitic diseases, the development of satisfactory biologic tests for tuberculosis and brucellosis, the knowledge concerning iodine deficiency in the new born pig and lamb and the many other technological developments in therapy, prophylaxis and control of diseases have all added up to result in better nutrition, better economy, and better land utilization through animal culture.

If there is a tendency to dispute the value of a sound, disease-free animal industry on the basis of the inefficient use of feedstuffs by first feeding the products of the land to animals and then to man, it should be remembered that when such practices have developed the people have declined markedly. Perhaps our greatest buffer against overproduction and ruinous rural economy lies in the very fact that animals can and do act to eliminate surplus feedstuffs which could not be fed directly to man with economic safety. This then represents a common ground between the diseases of animals and man from a purely cold blooded economic viewpoint.

From the public health standpoint, diseases of animals which may be transmitted to man are of primary consideration. However, here again the economic aspects are also important, but human suffering is even more paramount. There is, as previously stated, an imposing list of some 83 diseases which may be transmitted from animals to man. The more common of these are: anthrax, brucellosis, tuberculosis, glanders, leptospirosis, psittacosis, Q fever, Rocky Mountain Spotted fever, tularemia, rabies and parasitic diseases. These represent diseases which are spread in different ways; by direct contact, by insect vectors, by inhalation, by ingestion, and by indirect means such as contaminated water or soil.

Perhaps one example of the effects of practical control of one of these animal diseases would suffice to demonstrate the public health importance of such an effort. With the advent of a testing agent for tuberculosis, i.e. tuberculin, a program of bovine tuberculosis control and eradication was initiated in the United States based on testing and slaughter of all cattle which reacted to the test. After about 25 years of both intensive and extensive effort the last county in the United States was declared a modified accredited area for bovine tuberculosis in 1940.

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During and subsequent to the accomplishment of this stupendous task the incidence of bovine tuberculosis infection in man in the United States has decreased to essentially nil. This decrease occurred primarily in the bone, skin and glandular tuberculosis so common in children 30 to 40 years ago. It will remain for historians to record whether the results were worth the effort and cost. Reports indicate that 279,235,490 cattle were tested with tuberculin up to 1945 at a total cost of about $250,000,000. Considering the results achieved, the cost does not seem excessive. This then constitutes direct evidence of the common ground between diseases of man and animals.

Possibly a few words concerning preventive medicine, both veterinary and human medicine, would not be out of order. The ideal of medicine is the prevention of disease, and the necessity for curative treatment is evidence of its failure. From the earliest times, ways and means of prevention have constituted a part of human conduct in both diseases of man and animal. Comprehensive efforts to protect the millions who suffer economically and physically through disease of the animals they raise have not been made and there will be no change unless all of the medical and allied professions assume their responsibilities for preventive as well as curative medicine. Time may not be far distant when the animal husbandman, the poultry producer, the dog owner, and in fact the public at large will demand more and better professional advice about both sanitation and prophylaxis especially where concerned with those diseases of animals transmitted to man.

The practice of preventive medicine originated in the ancient world. Man in his spasmodic efforts to stop the pestilences which threatened to overwhelm him slowly learned that without knowledge he was without hope. Thus the history of preventive medicine is the history of seeking and finding of the essential facts. From the works of Pasteur, Koch, Theobald Smith and many others, there have followed a succession of discoveries which distinguish the age in which we live. The discovery of the disease producing bacteria was only the first step in establishing our knowledge. What did the bacteria do? What could prevent or control their activity? Through much brilliant work the concept was established that though the healthy body of man and animal may be subject to infection by a bacteria and suffer their toxic effect, the body may, of its own cells and fluids, build up defense, destroy and assimilate the invading organisms. Further efforts led to the discovery of viruses, antibodies and their place in body defense, and of arthropod vectors in the spread of infectious agents. Then lastly the discovery of compounds and antibiotics capable of destroying the parasite in the body completed the illustrious chapter. Prior to the age of "sulfa" drugs and antibiotics, there were very few satisfactory medicinal agents as cures for specific infectious disease entities. The advent of sulfa drugs and antibiotics ushered in a new era of combatting infectious diseases by specific cures. This new approach promises to be of much greater importance as it reaches its maturity in the years to come. Also the more recent development of hormone therapy, specifically ACTH and Cortisone, opens another promising avenue for combatting disease, infectious and non-infectious. Yet this is not the whole story. Men have learned that bacteria and viruses are unstable and variable in their functioning, and depend on many circumstances both within and outside the living body and their host.

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nature of disease. The concept of the contagious nature of disease caused the advances just mentioned. The reduction in the number of deaths due to infectious diseases attests to its value. Many of the aforementioned concepts and advances were made possible through research based on the common ground of animal and human diseases. Today the old doctrine that there is a single specific cause for each disease entity is not entirely tenable. A purely bacteriologic explanation pays little heed to the fact that health depends upon a complex series of related functions. The essentials of an infectious disease are two--an animal and an organism; these interact, react and are acted upon by external forces. The more quickly it is recognized that causation is a constellation of predisposing, provoking and perpetuating forces the more certain will progress be made. To reduce the approach to every disease to concern with only one provoking factor continues to retard progress. It is not enough to know that infection is present in the animal body; one must know what the characteristics of the invading organism are, whether it is present in great numbers or few, where and how it entered the body, where it operates in the body, and what are its other hosts, if any. For disease is a varying process, it is not a fixed entity. It may affect the whole body or only a special organ or tissue, but its actions begin in the cell. Checking and controlling it are inter-related not only with anatomy, physiology, pathology, clinical observation, post mortem examination, but the new applications of physics, of chemistry, of biology and of the fact that a common disease ground exists between species of animals including man.

Aside from the physical world there are communal factors which influence the incidence of disease. Density of animal populations, movement of groups, age and sex distribution, and environmental conditions such as domesticity and the attitude of the owner, govern the prevalence of disease in both animal and man. It has been stated that the occurrence, the distribution and the types of the diseases of mankind in distinct epochs of time, and at various points of the earth's surface will render an account of the relations surrounding the individual and determine his manner of life. This might well define the province of the science of epidemiology or eipzoology. In other words, man's dependency on animals has made his prey to certain diseases which he might not otherwise acquire.

Preventive medicine and especially its further extension and application in veterinary medicine can go a long way toward protecting mankind from certain diseases and also toward supplying man with his primary biological needs of food, shelter, health and enjoyment. The first stage is to give those conditions of food and surroundings now enjoyed by less than one-third of the world's population to the remaining two-thirds to enable them to reach a desirable standard of health. In order to bring food supply to an adequate level by 1960, which involves accommodating for an estimated 25 per cent increase in world population, production of the principal foods would have to be increased as follows: cereals, 21 per cent; root crops, 27 per cent; sugar, 12 per cent; fats, 34 per cent; peas and beans, 80 per cent; fruit and vegetables, 16 per cent; meat, 46 per cent; and milk, 100 per cent. There can be no question that a minimal application of science could increase the rate of agricultural production many times. Prevention of the continuous colossal losses due to disease of animals producing milk, eggs, meat and other animal food products would do much to alleviate potential food shortages. Until now many changes have been made but with largely commercial incentive, and though

nature of disease. The concept of the contagious nature of disease caused the advances just mentioned. The reduction in the number of deaths due to infectious diseases attests to its value. Many of the aforementioned concepts and advances were made possible through research based on the common ground of animal and human diseases. Today the old doctrine that there is a single specific cause for each disease entity is not entirely tenable. A purely bacteriologic explanation pays little heed to the fact that health depends upon a complex series of related functions. The essentials of an infectious disease are two--an animal and an organism; these interact, react and are acted upon by external forces. The more quickly it is recognized that causation is a constellation of predisposing, provoking and perpetuating forces the more certain will progress be made. To reduce the approach to every disease to concern with only one provoking factor continues to retard progress. It is not enough to know that infection is present in the animal body; one must know what the characteristics of the invading organism are, whether it is present in great numbers or few, where and how it entered the body, where it operates in the body, and what are its other hosts, if any. For disease is a varying process, it is not a fixed entity. It may affect the whole body or only a special organ or tissue, but its actions begin in the cell. Checking and controlling it are inter-related not only with anatomy, physiology, pathology, clinical observation, post mortem examination, but the new applications of physics, of chemistry, of biology and of the fact that a common disease ground exists between species of animals including man.

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they have resulted in greater yields of such products as eggs and milk, the expense has been the increase in incidence of animal disease.

Just as the artful politician can create public demand, so can trained individuals in the various medical professions create a public demand for preventive services. In this connection, two aspects in this educational program must be stressed with increasing emphasis. Although it is customary to measure the effect of a livestock disease on the basis of the monetary loss to those who own the animals and the cost to taxpayers who supply the funds for its prevention or control, the direct and indirect effects on human welfare are rarely measured. Some recent estimates concerning the staggering losses in milk and meat caused by Brucella infections reflect in no uncertain terms the manner in which one animal disease affects human welfare in general and the cattle and swine raising industries directly. As far as it is apparent, either such information has not reached the stock owner and the general public or they have failed to appreciate the broad social implications of it. To many, disease still seems something occult, supernatural, and beyond their understanding or control. Few are doubtless aware of how infection of livestock may affect their own families and the population at large. Significant epidemiologic and epizoologic data collected over the world are rarely interpreted to the man on the farm or to the owner of companion animals or to the public. Once animal owners and the public recognize that their acts or omissions may affect their own health and that in a large measure they have control within their power, preventive veterinary and human medicine will assume a more prevalent position. Education of the owner of animals and those contacting animals then becomes the instrument whereby strides can be made to minimize the effects of diseases on both man and animals. You, as trained specialists in responsible positions as teachers and research men, can and should aid in the dissemination of such knowledge for the benefit of human welfare.

Another area of common ground between the diseases of man and animals appears in the field of research. Many of our common day to day medical practices are based on the results of experimentation with animal diseases and abnormalities which have direct application to man. In your profession you are dependent upon animal products for the alleviation of numerous human ailments such as diabetes, glandular insufficiencies, treatment for arthritis, and numerous well known biologic agents. Not only do animals supply the substances, but they also were the proving ground for the efficacy of many of the substances.

Perhaps one current example of cooperative research on this campus would exemplify the common ground between animal and human diseases. As you know there are about seven million human arthritics in the United States alone which present an extremely difficult problem to solve. The etiology of arthritis is not well understood and any approach to a suitable solution to human arthritis without knowing the cause is definitely empirical and apt to be unsatisfactory. There is also a naturally occurring arthritis in swine, also of unknown etiology which apparently resembles rheumatoid arthritis in man. Hence with the cooperation of the school of pharmacy, the engineering experiment station, the department of animal husbandry and the department of veterinary science, research is underway to attempt to determine the possible relationship of this condition in the two species and to correlate the findings.

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THE RESEARCH GROUP IN INDUSTRY

Barbara B. Brown
The Wm. S. Merrell Company, Cincinnati, Ohio

During this week you have listened to and discussed ideas and attitudes on the training of students in pharmacology. Most of this has been concerned with instruction from the point of view of the educator. The participating members of this Seminar are, however, also responsible for the training of many future members of industrial research groups. Some of your students will be those who will be concerned entirely with pharmacology in one or more of its aspects. The Seminar recognizes the growing importance of industrial research, and it is actively considering the various approaches to training those who will enter this field. There is at the present time an unusually large demand for trained pharmacologists, and indeed for all degrees of pharmacologic training. In the future, not only will industry need increased personnel, but there will also be greater numbers of students anxious to enter the industry. The inevitable expansion of our science will be successful if, as during this week, the aims, objectives, methods, attitudes, and all possibilities of training are thoroughly analyzed.

By this time your discussions may have led to the conclusion that research goes along pretty much the same lines no matter where it is carried out. The essential requirements are proficiency in use of the experimental method and the abilities to discriminate and to cooperate. A discussion of the research group in industry will serve to picture the future scientist in a specific environment, how he works in it, and how the environment may influence him. An inside view of the structure and inner workings of organized pharmacologic research should give the teacher a broader understanding for his contact with students and some of the different types of problems they may encounter.

Research groups in industry are entities which can be described but they cannot really be defined to satisfaction. Group work came into existence with the first primitive specializations of man, and similarly, research workers banded together because specializations forced them to do so, and it was a means of extending their individual spheres of knowledge. The collective groups which are known as organized research continue to grow and multiply because no one man can cope with all the complexities of even any one small research problem today. But the mere mechanics of group work do not mean it will be productive. For group work has been productive only when full cooperation has been attained within itself and with its outside relations. Cooperation, since it is a human function, is a function of the character of the cooperating individuals. Thus both research ability and the cooperative attitude are the two primary requisites for smooth working groups. The exact type of research ability and attitude varies from organization to organization, but within a certain organization they are so important that their already existing character frequently determines the addition of new personnel.

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intelligence, and conditions for the use of it in constructive and creative thinking should not only be merely satisfactory, but should be optimal. The proper atmosphere comes about in industry by well-adjusted relationships with the outside influencing forces of the group, and in industry the most important relationship is with management. Since research organizations are generally considered to be the insurance of industry, management usually treats them with a reasonable amount of delicacy. In fact, management often assumes what might be considered a generous attitude toward research from the viewpoint of other laboring people. While it is of absolute necessity for management to supervise and to correlate, they are not dealing either with a type of work which can be rigidly outlined or one that can be directed specifically. Traditional utilitarian organization hinders human production just as much as no direction at all will fail to produce results. It is the balance between complete unsupervised freedom and strictly controlled conditions which has been found to produce the best results. In practice, a competent research director and his assistants are used as sort of a buffer system through which the aims of production can be accomplished with relative ease.

The group method of organization for research advancement was initiated and found to be successful by the research workers themselves, and industry has taken over the method with relatively little modification. Industry has not actually dictated how research should be organized, but it simply continues to make use of the natural development of group work. It is only natural that competition should select the best methods of operation.

Specifically in pharmacology, the present method of research organization has existed for only a fairly short period of time. Its evolution was not entirely spontaneous, or at least an important stimulus was applied with the enactment of the revised Food and Drug Act in 1938. The revised Act imposed severe restrictions on the introduction of new drugs and required much more extensive investigations than had hitherto been carried out generally. More personnel was necessary for the work, and new research groups were formed.

Somewhat along these same lines, industrial bidding for approval for their new drugs by the American Medical Association and other groups or institutions concerned with national welfare has been even further impetus to research expansion. Here is an instance where industrial competition has been almost directly responsible for increasing research facilities and personnel. Indirectly this competition has also aided in establishing the high standards which are increasingly characteristic of industrial research groups.

It should be stressed, however, that regardless of how group research has been originated, successful research depends upon the integrity of the research group, and that its rise or fall is the direct result of its internal structure and group character.

In pharmacology, as in any field composed of a number of related sciences, the actual organization of research groups follows naturally the different inner specialties which have grown up within it. Its divisions are the same as those in the logical sequence of investigation of new things. Follow, for instance, the course of investigation of a new drug. First, a large number of new substances are screened for particular types

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of pharmacologic activity. If an interesting substance is uncovered, the second step is to evaluate quantitatively each of its various desirable and undesirable actions, acutely and chronically. It may or may not be necessary to establish mechanism of action. When the pharmacologic character of the new substance has been shown that it should be therapeutically useful and a medical advantage, the third step is to establish its safety. Finally, after the new compound is put on the market it may be necessary to determine by means of bioassay that it lives up to claims made for it. Here are the four fundamental divisions of a pharmacology department.

Organization of the different groups follows the same lines. Let us consider first the groups which handle activity determinations. There may be many subdivisions if the particular company is large enough. There is the chemical type of pharmacology which may be concerned with the study of nutrition, drug metabolism, or basic biochemistry. Biochemical groups may also undertake the isolation or fractionation of active plant or animal tissue principles, but when this is an important aspect of the particular company, biochemistry is a separate division or department composed of its own specialty groups. Pharmacologic biochemists themselves are a necessary part of a pharmacology department, and their work is usually concerned with the methods for analysis of the new drugs and their metabolic products so that studies on the absorption, metabolism, tissue distribution, storage, and elimination of the new substance can be carried out. The second type of activity group is that which is concerned with pharmacodynamics. Here subdivisions are frequent and are according to the specialized problem at hand, such as cardiac, autonomic drugs, centrally acting drugs, etc. Then there may be additional groups handling activity work of a slightly different nature, the best example of which is endocrine research.

In all of the groups handling determinations of activity, the procedure is roughly the same. New synthetic substances are subjected to the screening program, in which a preliminary estimation of activity is obtained. Screening programs may be handled in different ways. Frequently screening is done by the various specialty groups as an integral part of their work. In other organizations, it may be the entire function of one group to carry out all screening tests for the rest of the department. Both systems have merit, the advantage of the first being that the specialty group may make important observations during screening and can carry along with them interesting formulas and unusual types of actions, while the advantage of screening being done by a special group is that it frees the other groups from routineness and time required by screening. Substances of possible interest selected by the screening procedures are then taken over by the groups which will investigate their actions. It is the function of these groups to find out how many pharmacologic or biochemical actions the new drug may have and to analyze these as far as possible. This means that not only will old known methods of evaluation be applied, but more frequently new methods will have to be designed.

Counting screening and activity determinations, including those of a chemical nature, as two research groups, the third major type of group is that which carries out the safety test or the chronic toxicity studies. An evaluation of safety or chronic toxicity is required for each new product and often for each of its modifications. This work is of the long-term nature since chronic toxicity studies are considered adequate only

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when they are made in at least two species of animals and over such periods of time as six months or a year. The work includes certain routine procedures, such as regular and constant checks for signs of toxicity in large numbers of animals, by following weight, blood, or other indices and applying various histologic and other technics. Here technics of procedure and evaluation must be fitted to or devised for each type of toxicological study of each new compound.

The fourth major group, the bioassay group, comes into play after the new drug is produced. Its chief duty is to check the potency and safety of each new batch of material. The greatest volume of bioassay work generally deals with determination of pyrogen in injectable materials and potency determinations of estrogens, digitalis, and like substances. Bioassay work is not all routine because it must often devise or routinize special tests for new drugs which cannot be otherwise analyzed.

The number of steps involved in complete pharmacologic evaluations certainly indicate the diversified activities and broad nature of pharmacology. When applied to industry, pharmacology means more than the simple definition of drug action. Each phase of pharmacologic determinations can become a specialty. From the standpoint of training, it would be impossible to cover all of these phases. Perhaps more important is the fact that even what appears to be routine in pharmacology actually keeps changing as new techniques or interests are developed. In every group it is necessary to do a fair share of basic research. This is naturally more extensive in some types of work than in others. Knowing the value of observations and the means by which additional information can be gotten is the most important. But all of the pharmacologists must to some extent be specialists in equipment, and it is most helpful to have had some experience in different types of gadgeteering. The most useful type of training then is one which gives a broad background. Proper knowledge of how to apply fundamentals to special instances allows the individual to make his own specializations. With the additional training he gets while working in industry, the individual will tend to emphasize one aspect or another of his previous training.

The internal management of research groups is built around just such types of persons who can apply the research method to a large number of various circumstances. Each research group is directed by an experienced research worker to whom they are completely responsible. The research group method of organization is so well established that the leader of the group is simply called a group leader or section leader. The group leader is chosen for his demonstrated ability to conduct and to lead research. But because his job also includes many administrative duties, he is also chosen partly for his ability to lead people and to cooperate. The work of the group leader is of three types: research itself, teaching, and administration. The amount of each of these which he is required to do depends upon the type of work and the size of the group. If it is a small group, or if he has an administrative assistant, he may be engaged entirely with the development of new techniques and investigations of new drugs. With either small or large groups he must be a teacher, giving instruction, on the methods of investigation and evaluation, on the rationale of the work, and on the significance of each piece of work. It is largely by his teaching that the group as a whole progresses and becomes more productive and useful. And it creates incentive and a feeling of accomplishment. The group leader is in an excellent position to teach for he is in constant close contact with his students. In fact, it is generally

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the hope of the group leader that responsive assistants or technicians will advance if already trained or will want to go back to school for the broad background which industry cannot give them.

The administrative duties of the group leader may encompass all sorts of things, depending upon the organization. First of all, he is responsible for the working conditions and attitudes of his group. He attempts to satisfy, as far as possible, the physical conditions for good work, and then he must see that his group gets along well together. Since he is usually part of management, he must carry out the policies of management. From the economic standpoint, he must use judgment in his expenditures in all phases--salaries, equipment, and time. He must view the nature of his work in a way which can help both the organic chemist and the pharmaceutical research groups, and he is often called on for his professional opinion as to the manufacture or promotion of new products. Thus he must cooperate with and have a working knowledge of the other divisions of the company.

But of course research is the priority job of the group leader. It is his job to conquer the new research project. He must see the pattern of the projected research, estimate its expense in time, effort, and money, and he must design the actual experiments. His experimental designs must be planned so that the results not only answer the scientific questions, but also why the results are significant, and in relation to what is known for similar endeavors. If the actual work is carried out by his staff, he must train them in each of new techniques, constantly supervise, and be alert to all interesting observations. Then, when the work is achieving its initial aim, it is the group leader who adds up the facts and the observations, puts them in order, checks and re-checks for completeness, and analyzes and re-analyzes. And then he interprets for himself, the group, and for management. His interpretation includes the formal reporting, a survey of all the meanings and implications of the problem, and suggestions for its disposal.

That sounds like a pretty big job for the group leader. It can be handled smoothly when one project is undertaken at a time. But the vagaries of research frequently make it feasible for two or more projects to be carried out at the same time. This almost automatically means that the size of the group becomes larger and the group leader has more administrative duties. If the group is sizeable, a second individual who has more training or qualifications than that of the technicians acts either formally or informally as the research assistant. He may either be responsible for the planning and collecting of details of the experiments, or if adequately trained he may carry out an entire project by himself. In either case he generally conducts most of the work himself. In our laboratories the research assistant is an individual with college plus training. He may or may not have a Ph.D. degree. He receives most of his specialized training on the job and after a few years may be in a position for advancement in his specialty or, if he has not already done so, to finish his formal education.

More commonly, and perhaps ideally, groups are not large enough to warrant a research assistant. Instead, the research man has one or two or more technicians which he handles directly. They may assist him in his experiments or may be assigned to tests which have become more or less routine. For after all, a great deal of research is of a routine nature.

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The administrative duties of the group leader may encompass all sorts of things, depending upon the organization. First of all, he is responsible for the working conditions and attitudes of his group. He attempts to satisfy, as far as possible, the physical conditions for good work, and then he must see that his group gets along well together. Since he is usually part of management, he must carry out the policies of management. From the economic standpoint, he must use judgment in his expenditures in all phases--salaries, equipment, and time. He must view the nature of his work in a way which can help both the organic chemist and the pharmaceutical research group, and he is often called on for his professional opinion as to the manufacture or promotion of new products. Thus he must cooperate with and have a working knowledge of the other divisions of the company.

But of course research is the priority job of the group leader. It is his job to conquer the new research project. He must see the pattern of the projected research, estimate its expense in time, effort, and money, and be must design the actual experiments. His experimental designs must be planned so that the results not only answer the scientific questions, but also why the results are significant, and in relation to what is known for similar endeavors. If the actual work is carried out by his staff, he must train them in each of new techniques, constantly supervise, and be alert to all interesting observations. Then, when the work is achieving its initial aim, it is the group leader who adds up the facts and the observations, puts them in order, checks and re-checks for completeness, and analyzes and re-analyzes. And then he interprets for himself, the group, and for management. His interpretation includes the formal reporting, a survey of all the meanings and implications of the problem, and suggestions for its disposal.

That sounds like a pretty big job for the group leader. It can be handled smoothly when one project is undertaken at a time. But the vagaries of research frequently make it feasible for two or more projects to be carried out at the same time. This almost automatically means that the size of the group becomes larger and the group leader has more administrative duties. If the group is sizeable, a second individual who has more training or qualifications than that of the technicians acts either formally or informally as the research assistant. He may either be responsible for the planning and collecting of details of the experiments, or if adequately trained he may carry out an entire project by himself. In either case he generally conducts most of the work himself. In our laboratories the research assistant is an individual with college plus training. He may or may not have a Ph.D. degree. He receives most of his specialized training on the job and after a few years may be in a position for advancement in his specialty or, if he has not already done so, to finish his formal education.

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A technician may or may not have some degree of training. It is most helpful, however, if he has an idea of quantitation, and this may have been attained by his having had some experience with mathematics, chemistry, or physics. Biological training is not a necessity, rather character is probably most important--some degree of intelligence, reliability and honesty in work, willingness, and above all, common sense.

This outline of research group organization has considered its members primarily as individuals. But a research group is a unit, a part of a department, a part of a scientific division, and a part of an entire company. It functions best when it functions as a unit, not as particular individuals. It doesn't have to live up to the old college try idea, but the group should try to attain a well-adjusted personality just as each individual does. A good team personality means that each of the members are well adjusted in their work and to each other. If the right material is in the group, good administration can produce good team spirit by making objectives clear-cut, and by well-defined division of the work. Each member of the group must be assured of his own importance in relation to the group and as the group is related to the whole organization. He must feel secure, and know, if he is interested, what opportunities might lie ahead. The quality of group spirit is so important in research that often character is counted as the most important attribute of a research worker. This I feel is an extreme attitude, but not an unusual one, and it seems to stem from the fact that smooth-functioning groups are more productive than groups of isolationists or ivory-tower occupants.

It is true that in some industrial houses not this much attention is paid to group attitude. Such institutions also require cooperation and good individual personalities. But all try to provide adequate incentives. In almost all industrial research organizations, publication of work is encouraged. To the individual, a publication often serves to increase his own personal prestige and is an indication of his research ability and standards. As such it is an incentive, for not only does the individual wish to contribute to his science, but he wishes recognition of accomplishment.

Participation in scientific societies, both regional and national, is also encouraged. In some research organizations there is a definite system whereby each research individual is sent to national meetings of organizations of their special interests. If the individual has accomplished a worthy piece of research, he may also be encouraged to present a paper at these meetings. It is a system similar to that used in educational institutions, although the freedom to discuss new work may differ with the company. Such participation in scientific societies is not solely for the benefit of the individual or simply to serve as incentive. Experience has shown that outside contacts with other scientific men and the direct awareness of what is happening in the particular science leads to better understanding of research and consequently greater productivity.

Most research workers feel that the challenge of a new problem is incentive enough for good work, but we must be practical too. Continued prospects of a good salary is a fine incentive, and in some places workers are additionally rewarded for unusual ideas or accomplishments.

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tacts are the library and the freedom to discuss problems and interests with other groups. All members of the group should use these contacts, for it is by means of them that they build their knowledge and increase their perspectives.

Departmental seminars have been found to be highly successful in the management of research organizations. In our department each member, including all research technicians, are responsible for at least two seminars during the year. They do not have to participate, but usually only brand new members of the department may fail to do so. There is complete freedom in choice of subject, but as a rule each member takes pride in presenting his own work. It is a valuable opportunity to present material in a way in which others will understand it, and it generally makes clear the exact value of the work done. Seminar discussions frequently yield the new idea needed to go ahead with a piece of research, new slants, and even the evolution of new procedures.

A further incentive to greater productivity may be in the origination of new research projects. When a research project arises within a group, it is usually attacked with unlimited zeal. It would seem reasonable that new projects should come from the research worker since he is in close contact with the science and he has the opportunity to keep up with new advances. But the group should be reminded that it takes a great deal of judgment to select new work, and of course just this attitude may be incentive enough to produce well-defined, carefully thought-out new ideas.

My description of the environment of the research group in industry may sound to some like a veritable utopia for the research-minded. It is true that in many situations it may be ideal. Nor can it be denied that in some places red tape, rules and domination are hard to take. An outline of the restrictions encountered in industrial pharmacologic research is one of the last things to be considered, simply because company restrictions are generally considerably less important than any of the other factors influencing group research. Relatively few of the functions or responsibilities of the group are definitely planned, and I believe you will see that in general these could scarcely interfere with the way in which a research man desires to conduct research.

First, each member of the group is required to be regular in his working hours. This is both a way of preventing laxity and of preventing discrimination among the different categories of workers. While at work, however, the research worker utilizes his time as he sees fit. The only requirement is that his work will be useful or productive within a reasonable period of time, but of course this is one of the general aims of research. Much research workers spend much more time in their work than is actually required and this is appreciated by the company. Sometimes, there is a tendency for management to be somewhat lenient as to time-off; although this too must be regarded with considerable common sense.

Next, those in research groups are required to keep records of all their work, and this is only good scientific procedure. Then they must write reports in such a way that management is always informed on what they are doing and what it means. Report-writing may seem tedious to the individual, but as a scientist he must know how to explain his work and its meaning, this is an excellent way in which to get such experience.

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The assignment of certain research projects may also tend to limit freedom in research. I personally feel that this is more likely the result of an individual's attitude, for interesting research is everywhere. An assigned problem may be tremendously interesting and have many possibilities. If it doesn't, there may be one of two faults. The investigator may not be research-minded, or, if he is, it is up to him to determine that the problem is at fault and why there are no possibilities. The disposal of such a problem is then obvious.

Less precisely tangible of organizational requirements is the duty of all members of the group to follow the established channels of administration and to keep their superiors informed on all matters regarding group activity and attitude. Any hidden activity or undesirable attitude or any overstepping of bounds may be disastrous to the personality of the group and consequently to its work.

Finally, each group must keep in mind that it must act as a service department to all other groups. This is a matter of group cooperation and although at times a particular service may seem to be a chore, its accomplishment may still have its rewards. It must be remembered that a company depends upon its interrelationships.

Probably the best way to sum up this description of research groups in industry is to say that research is most productive when it is carried out by cooperating groups. In pharmacology the organization follows its own general divisions and subdivisions. Each group has more or less specialized interests. Its individuals have varying degrees of pharmacologic training and research ability; all must have the ability to work with others. Each research group is fairly autonomous within itself, but it must balance and be balanced with its responsibilities to management, and it must cooperate with other groups both inside and outside of its own department.

The research group of industrial pharmacology is one of the research environments in which some graduate students will find themselves. It will have great appeal to some and some may do their best in such an organization.

There are various types of opportunities offered to young individuals with graduate training in pharmacology by the research group system in industry. Depending upon the emphasis in their training, these individuals may fit best into one or another of the natural divisions described. That is, some may have had special training or be especially capable in the chemical aspects of pharmacology. For others, their training, experience and special aptitudes may suggest that they would best fit into groups evaluating the possible toxic effects of prolonged administration of drugs, and actually this work is broader than one might imagine.

Others may find themselves in biological control laboratories. Development of new control procedures and the re-working and improvement of established procedures requires proficiency in pharmacologic research.

The variety of activity in pharmacology in industry as operating under the group system indicates the many types of work which can fit a variety of individuals based on special emphasis during their training period and special aptitudes of the individual. Frequently, and probably desirably, most of these aptitudes will have been developed before the student enters graduate school, and in general his training in graduate pharmacology should aim to make him a well-rounded person, capable of conducting research and of thinking in terms of all of the basic medical sciences, including biochemistry, physiology, pathology, and histology, and he should be capable of bringing knowledge of these fields to bear on the problem he is confronted with in pharmacology.

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FUTURE MANPOWER NEEDS IN PHARMACOLOGICAL TESTING, CONTROL, AND RESEARCH

Glenn L. Jenkins
Dean, Purdue University School of Pharmacy
West Lafayette, Indiana

The future manpower needs in the area of pharmacology are difficult to predict; in fact, it is difficult to determine how many individuals are now engaged in pharmacological work. We have available the fact that in 1950 the membership of the American Society of Pharmacology and Experimental Therapeutics consisted of 456 members. This prima donna group, however, represented only a fraction of those engaged in pharmacological endeavors of one kind or another. Because there has been a marked shortage of well qualified pharmaceutically trained individuals in the past, much pharmacological investigation is being carried on by biochemists, bacteriologists, mycologists, pharmacists, physiologists, endocrinologists, and others. In our considerations it is necessary to remember that pharmacology is a man-made science and that in modern times the sciences tend to cut across the borderlines and, just as the pharmacologist may practice many other sciences, many other scientists may practice in certain areas of pharmacology.

The best basis for predicting future needs was made by Smith (Problems in Postwar Education--Scientific Training for Democratic Leadership, Chem. and Eng. News, 23, 338-344, 1945). He points out that from the beginning in 1905 when there were in this country but three industrial research laboratories, the number grew to 297 in 1920 with a scientific personnel of 7400, and to 2350 laboratories in 1940 with a scientific personnel of 70,000. Of this latter number nearly one-half of all professional research personnel in industry were chemists. He pointed out that if these figures are extrapolated, they lead to the expectation of about 3,500 laboratories in 1950 with a scientific personnel of about 150,000. This estimate has proven quite correct. If we further project the figures to 1955, we may well estimate that by that time there will be 5,000 laboratories with a scientific personnel of about 200,000. Applying such predictions to pharmacology, we can expect an increase of about 25 per cent by 1955 in the necessary scientifically trained personnel.

We know that there are approximately 11,000 firms engaged in some area of pharmaceutical manufacturing in the United States. Some 50 or 60 of these firms maintain what may properly be called pharmacology departments staffed by a single individual or with five or ten competently trained scientists with several technicians and assistants. In my opinion, two or three hundred of these firms engaged in manufacturing could well utilize qualified personnel in the area of pharmacology if such personnel were available. In our pharmacy schools probably no more than twenty per cent are adequately staffed for pharmacological instruction. In those schools that do have well established pharmacology departments it is expected that expansion will occur. For example, it is our expectation that our physical facilities and staff for instruction in pharmacology at this institution will be doubled in the next five years.

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In conclusion, I believe that we can safely agree that there will be a continuing and expanding need for well trained and competent individuals for pharmacological teaching, control and research. If we take care to make certain that individuals trained are exceptionally well qualified and highly competent, the continued growth and opportunity will be assured. The prime task in this area before our schools of pharmacy is to place emphasis on quality rather than quantity.

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THE STANDARDS OF THE AMERICAN COUNCIL ON PHARMACEUTICAL EDUCATION

Richard A. Deno
Director of Educational Relations, American Council
on Pharmaceutical Education
Rutgers University College of Pharmacy

The standards of the Council currently in effect are found in the booklet "Accreditation Policy and Procedure." The current edition of the booklet is the fourth. It has been in effect since November 1, 1948. A first draft of the fifth edition has been prepared and is now being submitted to scrutiny by the members of the Council. It will later be sent to the deans and to the board secretaries for criticism. An open hearing will be held later, and eventually a revision will be approved by the Council. It is not probable that the effective date of the fifth edition will be prior to July 1, 1952.

On page 11 of the current standards is found the much-debated requirement concerning five departments, effective July 1, 1952. One of the five is a department of pharmacology. An important second paragraph of this section provides that, "deviation from this requirement, necessitated by University organization, will be permitted only when it is clearly shown that the content and application of the instruction involved is of a character fully to meet the needs of professional pharmaceutical education."

This deviation clause obviously takes care of those instances where pharmacology for students in pharmacy is given in a medical school. It also covers the single case where pharmacology is taught in the biology department of the university. It allows also for a combination of pharmacognosy and pharmacology in one department. In such a case, the Council must be shown that undergraduate instruction in neither discipline suffers as a result of the combination.

On page 12 of the current standards are found the specifications for qualifications of staff members. The pharmacologist must have at least two years of graduate study in pharmacology, "or a corresponding amount of technical or professional training or experience."

Requirements of the Council on curricular matters are intentionally indefinite. A statement on page 14 of the current standards says that the latest edition (1945) of the Pharmaceutical Syllabus may be followed. Little or no attention has been paid to the Pharmaceutical Syllabus in the latest tour of examinations of colleges. Reference to the Syllabus will undoubtedly be omitted from the fifth edition of the standards. I do not believe that any rigid curricular requirement will be substituted. Instead, an indication of core requirements with further indication of the necessity for balance may be included.

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Finally, the general statement at the top of page five is applicable to pharmacology, as it is to all courses of a college.

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In conclusion, may I say that, important as the published standards are, of equal or greater importance is the manner in which they are administered. The term "standards," as used by the Council, implies neither uniformity nor inflexibility. The Council may have erred in judgment from time to time. It would be strange indeed if no mistake had ever been made. However, by and large, the record over the years is one of constructive and wise application of the published standards. If improvement in the undergraduate teaching of pharmacology, college by college, is as great during the next six years as it has been since the end of the war, the colleges as a whole will come close to meeting the letter of the Council standards.

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THE COMBINED PHARMACOLOGY-PHARMACOGNOSY DEPARTMENT

Nellie P. Watts
New England College of Pharmacy
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In some schools of pharmacy, pharmacognosy and pharmacology, with their subtending courses, are taught in the same department. In certain instances, this department is known as the Department of Biology; in other cases, as the Department of Materia Medica; in our school, (The New England College of Pharmacy), it is called the Department of Pharmacology and Materia Medica.

The teaching of these two subjects in the same department offers advantages and disadvantages. In order that one may consider these, it is first necessary that the subjects be defined. Viewed historically, the subject matter of each is not in much dispute. The term "pharmacognosy" (knowledge of drugs) was introduced by Seydler in 1815. This was prior to the time of the isolation of the alkaloids, and by custom, the subject pharmacognosy is the science of crude drugs — animal, mineral, or vegetable. It is a subject of natural history - used in the sense of accumulated knowledge - and includes:

1. identification — macroscopic, microscopic, chemical, and physical;
2. components — average yields of the constituents more active in therapy; and diverse items of
3. factual knowledge — source, part used, synonyms, methods of increasing yields, methods of extraction, commerce, and lore.

Pharmacology (science of drugs) is an equally old term; and during the latter part of the last century, it developed into an experimental science, using the methods of physiology to study the actions of drugs on living systems. Essentially, pharmacology is the science of the action of chemicals on living systems, and includes the nature and properties of these chemicals (drugs).

Used in the broadest sense; materia medica, pharmacognosy, and pharmacology mean the same thing — all knowledge about drugs. In a more restricted sense; pharmacognosy is concerned with the production of crude drugs; pharmacology is concerned with the actions of pure chemicals on living systems; and the term "materia medica" is becoming obsolete.

Since both pharmacognosy and pharmacology are subjects of applied biology with respect to drugs, there are <u>advantages</u> in their being taught in the same department. All members of the teaching personnel of the department can be expected to have some training and experience in biology. Much of the equipment for the two courses — for instance, special glassware and microscopes — may be used in common. Therefore, an economy can be expected to result from the teaching of the two courses in the same department.

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THE COMBINED PHARMACOLOGY-PHARMACOGNOSY DEPARTMENT

Nellie P. Watts
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Boston, Massachusetts

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is an advantage to a pharmacologist to have an understanding of the components of crude drugs. Also, a knowledge of pharmacognosy gives to a pharmacologist information on sources of the same or similar chemical substances -- for instance, the macromolecular carbohydrates.

Within a department, the subject matter of the courses can be more strictly defined and responsibility for the teaching of the subject matter may be more easily allocated than when courses are given in different departments. In illustration, I refer specifically to "uses" of drugs. "Uses" are taken up in many courses in addition to the two being discussed here. A pharmacy student usually just memorizes "uses," then he confuses them, for he is seldom able to relate this information to previous knowledge. It is also true that many people prefer to teach and discuss the unusual -- the novel -- rather than the usual. "Uses" are more easily and more effectively taught in pharmacology than in any other course in the pharmacy curriculum, for here they can be taught on the basis of the effect of the drug on the physiology of the body. This is a logical and reasonable approach. Thus, "uses" are more easily remembered by the student, and overlapping of subject matter may be obviated by omitting them from the pharmacognosy course.

Although pharmacognosy and pharmacology are subjects of applied biology, their being terminal, major and divergent subjects of applied biology make their inclusion in the same department disadvantageous. Pharmacognosy is concerned mainly with problems in the production of drugs. Pharmacology is concerned with the effects of chemicals on the functions of cells and this science is employed in an effort to find better drugs to use against disease. Therefore, the training, interests, and abilities of capable teachers in each field will be different.

A teacher may take time away from his major subject to become better in the second. Such an action results in his being a poor teacher in each. He may concentrate on his major subject and give little attention to the second. This is obviously unfair to his students.

In summary, the advantages of a combined pharmacognosy-pharmacology department are largely those of economy. The disadvantage of such a combination is chiefly a reduction in the quality of production of the faculty (teaching and research) in an effort to cover two major and divergent subjects. To do so well requires a faculty of two specialties, gives the department two pinnacles, and results in an unwieldy administrative unit in the school.

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SUMMARY OF FINDINGS OF THE SEMINAR

L. D. Edwards, Professor of Pharmacology
School of Pharmacy, Purdue University
Lafayette, Indiana

The findings of the Seminar may be enumerated as follows:

(1) A definite need for a thorough understanding of pharmacology in professional pharmacy practice has been established.

(2) The main objective of the undergraduate course in pharmacology is to supplement the training of the pharmacist to the end that he will be a more valued member of the health team.

(3) The minimum biological prerequisites for the undergraduate course should be standard university courses in general biology, comparative anatomy, histology and physiology. These courses must be presented by the curriculum in a logical sequence.

(4) In didactic and the laboratory contents of the undergraduate course, some variance from school to school may be expected, but the instruction must be of sound quality and quantity. Combined departments of pharmacology and pharmacognosy are undesirable and are becoming obsolete; however, for administrative reasons the combined departments that now exist may be expected to continue for some time. Such combined departments should include professional teachers in both the areas, namely pharmacology and pharmacognosy.

(5) The pharmacology instruction of pharmacy students in a medical school department is dependent upon both the pharmacy school and the medical school. Such instruction can be completely satisfactory.

(6) There is still a need in pharmacy for well qualified pharmacology instructors and in industry and governmental agencies for pharmacologists in control and research.

(7) The presentation of pharmacognosy as a biochemical discipline would greatly enhance its value as a foundation course for pharmacology.

(8) Many other areas of instruction have much to offer the pharmacologist, i.e., biochemistry, endocrinology, statistics, microbiology, nucleonics, animal sciences, toxicology, etc. All such areas of instruction should be used to the fullest possible extent.

(9) Graduate instruction in pharmacology must be maintained on a high plane, and should be attempted only where proper supplementary courses and library facilities are available. Graduate courses in the pharmacology area may include the following: (1) advanced pharmacology, (2) drug screening, (3) bioassays, (4) experimental animal surgery and (5) toxicology.

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(10) Student selection both at the undergraduate and the graduate levels requires attention.

(11) State Boards of Pharmacy should be urged to examine candidates in the pharmacology area.

(12) A full appreciation of the value of teamwork among the industrial, medical and pharmaceutical pharmacologists would be most beneficial to all. The cooperation at this seminar is a case in point.

(13) The conduct of research in pharmacology on a team basis both in the schools and in industry appears to be most productive. The schools and industry should foster the inclusion of representatives of both areas on some of these research teams. Every effort such as grants, seminars, exchange of reprints, etc., are urged to develop cooperation between schools and industry.

(14) The American Foundation for Pharmaceutical Education, The American Council on Pharmaceutical Education, The American Association of Colleges of Pharmacy, and The Pharmaceutical Survey must receive much of the credit for the recent advance in the instruction of pharmacology in the pharmacy schools.

(15) Teachers of pharmacology in pharmacy schools should qualify for and join the American Society for Pharmacology and Experimental Therapeutics.

(16) Schools of pharmacy should establish pharmacology departments with adequate facilities and equipment and a competent staff to upgrade the quality of instruction.